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Fatty Acid Incorporation into Human Adipose Tissue (FIAT) in Hypertriglyceridaemia

Methodological clinical and experimental studies

By Göran Walldius

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By

Göran Walldius

To Eli abeth and our Johan and Joakim for their loving support and understanding in the past the present and in the future

This thesis is based on the following papers:

I Lars A Carlson Ingvar Eriksson and Göran Walldius: A case of massive hypertriglyceridaemia and impaired fatty acid incorporation into adipose tissue glycerides (FIAT) both corrected by nicotinic acid Acta med scand 194:363 1973

II Göran Walldius and Paolo Rubba: A micro-method for determination of fatty acid (FIAT) and glucose (GLIAT) incorporation and lipolysis in vitro in needle biopsies of human adipose tissue Scand J clin lab Invest In press 1976

III Lars A Carlson and Göran Walldius: Fatty acid incorporation into human adipose tissue in hypertriglyceridaemia Europ J Clin Invest 6 195 1976

IV Göran Walldius Serum triglycerides and fatty acid incorporation into human adipose tissue (FIAT) Their relation to adipose tissue characteristics and glucose tolerance Acta med scand In press 1976

V Göran Walldius Comparison of fatty acid (FIAT) and glucose (GLIAT) incorporation into human subcutaneou and omental adipose tis ue Acta med scand In pre s 1976

VI Göran Walldius Nils-Olov Theve and Paolo Rubba: *Inverse correlation between the rate of lipolysis* and fatty acid incorporation into human adipose tissue (FIAT) in vitro Studies with stimulation and inhibition of lipoly i Acta med scand In press 1976

The papers will be referred to in the text by their Roman numerals as listed above

CONTENTS

Hypertriglyceridaemia is often associated with and may predispose to development of atherosclerotic diseases such as myocardial infarction and intermittent claudication (2 17 20 21 22 23) Successful treatment of biochemical and clinical manifestations of these diseases depends on an understanding of their pathophysiological mechanism(s) There is now evidence to suggest that hypertriglyceridaemia may be due to a defective metabolism of triglycerides in peripheral tissues such as muscles and adipose tissue

The present methodological clinical and experimental studies were undertaken to investigate one previously never studied mechanism in connection with hypertriglyceridaemia which may be involved in the control of the uptake and incorporation of circulating triglyceride-fatty acids into adipose tissue Defects in this process may be associated with and perhaps contribute to development of hypertriglyceridaemia

There are several different mechanisms by which hypertriglyceridaemia may develop Increased intake of fat may give rise to hypertriglyceridaemia Endogenous hypertriglyceridaemia may develop when the hepatic synthesis and release of triglyceride-rich lipoproteins to blood is increased The hepatic synthesis of triglycerides depends among other things on the inflow of free fatty acids to the liver and therefore indirectly on the rate of fat mobilizing lipolysis in adipose tissue (22 53 56 57 64)

Hypertriglyceridaemia may also develop when the rate of removal of triglycerides from plasma to tissues is reduced (14 15 31 33 63 64) Low removal rate often expressed a fractional removal rate (14 15 63) may be due to decreased activity of lipoprotein lipase in various tissues (33 52 62 65) This enzyme is active in the capillary wall in the tissues and it liberates fatty acids from circulating exogenous or endogenously synthesized triglycerides These fatty acids must then be taken up by the fat cell as discussed below Low removal

rate has almost invariably been ascribed to the malfunction of this/these enzyme(s) Lipoprotein lipase activity is almost always extremely low in the rare type I hypertriglyceridaemia which is characterized by chylomicronaemia (16 33 40) Removal of circulating triglycerides is also reduced in moderate forms of hypertriglyceridaemia that is type II B III IV and V (according to Fredrickson s typing system as modified by WHO (4)) It has also been claimed that the activity of lipoprotein lipase is lower than normal in these types of hypertriglyceridaemia (13 29 33 52) There are however conflicting reports on the role of lipoprotein lipase in these moderate types of hypertriglyceridaemia a discussed below It is obvious that hypertriglyceridaemia may develop when either production or removal or both of these processes are out of balance

Several different methods have been used to study removal of triglyceride either in vivo or in vitro The so called intravenous fat tolerance test in which chylomicron like particles (Intralipid[R]) are infused intravenously has been applied to study removal of exogenous lipids in different types of hypertriglyceridaemia This has repeatedly shown a low fractional removal rate in all types of hypertriglyceridaemia (14 63) The removal of labelled endogenous serum triglycerides is also lower than normal in hypertriglyceridaemic subjects (15 63 64) and correlates directly with the fractional removal rate obtained by the fat tolerance test (63)

Lipoprotein lipase has been determined by various techniques in which the enzyme is relea ed from the capillary walls of several tissues including adipose tissue and muscle by heparin infused intravenously (13 33 52) However heparin also releases other lipases of different origin that hydrolyze mono- di- and triglycerides and also phospholipids (for review 33 59) The major lipase activities are those hydrolyzing triglycerides that is so called hepatic or salt resistant lipase activity They may be differentiated by in vitro techniques

The most common procedure is to inactivate postheparin total lipolytic activity with 1 M NaCl or protamine to obtain lipoprotein lipase activity These techniques have confirmed that lipoprotein lipase activity is low in the severe type I hypertriglyceridaemia However in moderate forms of hypertriglyceridaemia the postheparin lipoprotein lipase activity is often within normal limits (13 33 52)

Lipoprotein lipase activity has also been measured in biopsy specimens of human adipose tissue Various assay methods have been used Very low activities have been found in type I hypertriglyceridaemia (33 39) It has also been claimed that the adipose tissue lipoprotein lipase is sometimes low in moderate types of hypertriglyceridaemia (33 61) although normal values are often found Furthermore some of these studies have been criticized because the specificity of the substrate used has not been well defined (59)

The fatty acids liberated from the circulating triglycerides by lipoprotein lipase are offered to the adipocytes for uptake and incorporation Since several studies have shown that adipose tissue lipoprotein lipase activity may well be within the normal range in some subjects with hypertriglyceridaemia it may be possible that in those with normal lipoprotein lipase activity it is the fatty acid uptake and incorporation into adipose tissue rather than the activity of lipoprotein lipase that is rate limiting in the removal of triglyceride-fatty ac ds from extracellular sites into adipose tissue

The present studies were designed to study the possible role of the rate of fatty acid incorporation into adipose ti sue called by us FIAT in different types of extreme and moderate hypertriglyceridaemia The most adequate design of such studies would have been the measurement of the different steps involved in the disappearance of triglyceride-fatty acids into adipose tissue n vivo This would implicate both the fir t metabolic step related to lipoprotein lipase activity and

the second - the FIAT process Such studies are however difficult to perform In order to bypass the lipoprotein lipase step and exclusively look at the fatty acid incorporation process we developed an in vitro method in which the rate of incorporation of labelled fatty acids into adipose tissue was measured Labelled fatty acids have been used by many investigators to study the rate of triglyceride synthesis in adipose tissue (8 9 11 34 74 75) However we differ in our use of these labelled fatty acids and in interpretation of our results because we are interested only in the uptake and incorporation into adipose tissue of these fatty acids and not the absolute rate of triglyceride synthesis which involves additional metabolic pathways (11 34 74 75)

-glycerophosphate generally generated in the glycolytic pathway is the most important intracellular acceptor of fatty acids in the esterification process (11 34 75) A low formation of -glycerophosphate may be one possible explanation for a low FIAT activity and may be a common factor in hypertriglyceridaemia since in these subjects glucose metabolism i often impaired (1 11 26) By simultaneously measuring the FIAT process and the rate o glucose incorporation into adipose tissue glycerides called GLIAT which reflects the formation of -glycerophosphate from extracellular glucose it may be possible to quantitate the role of carbohydrate metabolism in adipose tissue n the FIAT process

Adipose tissue stores large amounts o triglyceride-fatty ac ds which may be mobilized in the lipolytic process In certain conditions such as stress exercise and prolonged fasting local release of catecholamines as well as circulating hormones activate the hormone sensitive lipase via the cyclic AMP-system (11 18 53) and fatty acids and glycerol are released Glycerol release is often taken to indicate the rate of lipolysis This lipolytic process may interfere in the esterification process of fatty acids (74 75 76 79) and possibly also in the FIAT-GLIAT process

Many studies have emphasized the important role of

Sweden) was used and applied at the margin of the incision In this study subcutaneous fat from other patients was also taken under general anaesthesia In the studies in papers III V and VI subcutaneous and omental adipose tissue were taken under general anaesthesia Blood samples and biopsies were taken after an overnight fast in the morning at the beginning of the operation No local anaesthesia was used Subcutaneous fat was usually taken above the umbilicus The intraabdominal fat was taken from the distal part of the greater omentum After the biopsy had been obtained the fat was transferred to a buffer solution (see below)

One percent of Xylocain^R (about 0 2-0 4 ml) was injected intradermally when the micro-method was used (papers II III IV V and VI) Needle biopsy specimens were taken from the subcutaneous fat of the lower abdominal wall at McBurney s point For the needle biopsies a 2 mm (external diameter) wide needle was attached to a vacuum-proof plastic syringe and inserted 4-5 cm into the superficial portion of the fat About 100-150 mg were recovered for further analyses Details are given in paper II

B Preparation and incubation procedures

Fat obtained at operation or by needle biopsy was transported in a buffer containing albumin glucose and fatty acids The specimens were freed from visible connective tissue preincubated for half an hour and then incubated in a freshly prepared buffer solution to which ^{3}H palmitic acid and ^{14}C glucose were added in tracer amount In the macro-method 4-6 specimens from each patient in total about 200-400 mg were incubated in 4 ml of medium In the micro-method the specimens were incubated in triplicate in 1 ml of buffer each specimen weighing about 30 mg Incubation time was 2 hours and the temperature was +37^{o}C After incubation the specimens were washed in saline to remove contaminating labelled fatty acids and glucose They were then homogenized and

glycerides extracted into heptane-isopropanol-KOH and washed once with this solution The ^{3}H-activity which is only activity in fatty acids (see below) and the ^{14}C-activity which is only activity in glyceride-glycerol (see below) were then determined in a liquid scintillation counter In order to compare FIAT value with GLIAT values on a molar basis the FIAT activity was divided by three and the glucose activity multiplied by two This is based upon the assumption that ^{3}H is incorporated into triglycerides and that two moles of -glycerophosphate are formed from one mole of incorporated glucose In the studies referred to in papers II and VI the values were also expressed as fractional removal rate

In the micro-method but not in the macro-method we also determined the rate of lipolysis which was measured as the release of glycerol (78) and release of fatty acids (46) FIAT values were corrected for isotopic dilution according to the formula of Dole (30) (paper II III and VI)

II Other methods

Separate specimens obtained in the same needle biopsy were used for determinat on of fat cell diameter according to Sjöström et al (69) The mean fat cell weight and fat cell surface area were calculated (68 69) Total fat cell number in the incubated specimens were obtained by dividing the weight of the tissue by the mean fat cell weight Value for total fat cell number in the body was obtained by div ding the amount of body fat calculated from a formula used by Persson (61) by the estimated mean fat cell weight

The fatty acid pectrum of the extracted glycerides was determined by gas liquid chromatography of the methylated fatty acids (paper IV) The different fatty acids were identified by comparing their retention time with known standards

Intravenous gluco e tolerance tests were performed as described by Ikkos and Luft (48) (paper IV)

Serum triglycerides (51) and cholesterol (12) were determined by semiautomated methods using an Auto Analyzer Technicon II In all subjects studied in papers III and IV the type of lipoprotein pattern was determined according to the WHO criteria (4) as described (19) When lipoproteins were not measured the type of lipoproteinaemia was assigned from the values of total serum triglycerides and total serum cholesterol (paper III)

Statistical calculations were performed according to Snedecor and Cochran (72) Since many of the variables were skewly distributed to the right they were transformed to logarithmic values before statistical calculations were performed (papers III and IV) All calculations in papers III and IV were performed by a 370/155 IBM computer Stepwise regression analyses was performed according to program BMD02R (see paper IV)

III Methodological errors

The methodological errors for the different methods used are presented in papers I II and III The average error of a single incubation and the average error in one subject as determined by the micro-method were respectively 10 7% and 5 8% for FIAT 11 1% and 6 2% for GLIAT 15 2% and 18 6% for glycerol and 5 4% and 2 2% for the determination of fatty acids Since there is a combined error in the determination of fatty acid release or uptake this error amounts to about 30% (paper III) The errors for the determination of serum triglycerides and serum cholesterol were 3 6% and 2 8% and the errors for the determination of fat cell size were 2 0% and fat cell weight 7 1% The error for determination of fatty acids by gas liquid chromatography was below 2% when duplicate analyses were performed on extracted adipose tissue

RESULTS AND COMMENTS

I Methodological studies (papers I II and VI)

A Anaesthesia, preparation and incubation

Our first studies (paper I) were performed on surgically obtained fat Specimens of about 200-400 mg weight from each patient were incubated The influence of local anaesthetic agents on FIAT and GLIAT was tested (paper I) by incubating adipose tissue with different concentrations of Xylocain[R] FIAT and GLIAT were not affected by any concentration nor was basal glycerol release when 30-200 mg fat was incubated in the micro-method These results are in accordance with previous findings (3 11 35 79) General anaesthesia was used in some studies (papers I V and VI) This procedure may or may not (11 54) affect some variables in adipose tissue metabolism

The effects of storage of fat for up to 4 hours at 18-25°C was tested This period of storage did not affect FIAT-GLIAT or glycerol release All these findings helped to simplify the procedure in the conditions often existing in practice

Preincubation was carried out after the fat was freed from visible connective tissue This procedure allows intracellularly accumulated fatty acids or other products to be released from the cell and the tissue specimens regain their metabolic activity (79)

B Extraction, recovery and distribution of radioactivity

Free fatty acids were washed away before and during the extraction procedure and were present only in insignificant amounts (less than 1%) in the glyceride extract used for calculating FIAT and GLIAT

Studies on recovery of various added compounds were performed About 100% of added di- and triglycerides were recovered in the final glyceride extract but only 50% of added monoglycerides and about 10% of phospholipids were recovered

When fat was incubated for two hours and all lipids

was no change in the fatty acid composition of the medium (paper /I) Hence it was possible to use this acid as a tracer and apply the correction formula of Dole The correction factor for FIAT was highest at highest rate of lipolysis

However we do not make a correction for possible intracellular dilution because as we previously discussed it was not our purpose to determine the absolute rate of triglyceride synthesis or the rate of reesterification

D Regional studies

It is well known that there are differences in adipose tissue morphology and metabolism between various regions of fat especially in subcutaneous and omental fat (11 25 32 38 45 55 70) This raises the possibility that FIAT-GLIAT and rate of basal glycerol release also vary between sites It is then important to know whether fat from McBurney s point is representative for other regions of adipose tissue In paper V we studied this aspect by taking biopsies during operations simultaneously from the abdominal wall and from the distal portion of the greater omentum We found that FIAT and GLIAT activities in omental fat were always about 40-50% higher than in subcutaneous fat A similar relation was found in subjects with low FIAT values especially hypertriglyceridaemic subjects and in people with high FIAT values There was some tendency for a higher basal glycerol release in subcutaneous fat but this was statistically not significant

It is unlikely that the higher FIAT values in omental fat can be explained by lower rate of lipolysis as discussed in paper V The higher FIAT and GLIAT values in omental fat could be related to the greater cell surface area in omental fat as suggested by our findings of a direct correlation between FIAT and fat cell morphology

(paper IV) Although we did not measure fat cell size in paper V we have now measured this variable in a subsample of those patients (n=12) studied in paper V Average fat cell diameter in omental fat was found to be 69±4 μm and in subcutaneous fat 87±4 μm This difference is highly significant (p 001) and confirms earlier observations (11)

The regional differences between other sites were further examined Data from these analyses are presented in Table I During operation needle biopsy specimens were taken from different subcutaneous regions as well as from omental fat Highest FIAT and GLIAT values were obtained in omental adipose tissue The values for different subcutaneous sites were lower but did not differ

Table 1 FIAT GLIAT and glycerol release from omental fat and from different subcutaneous regions from 14 subjects[1)]

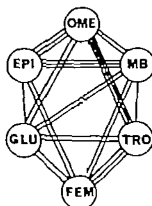
		OMENTAL	EPIGASTRIC	GLUTEAL	FEMORAL	TROCHANTER	Mc BURNEY
FIAT	mean	140	65	105	[illegible]	[illegible]	82
([illegible]/g/hr)	sem	22	9	16	13	7	15
	range	40-325	29-138	[illegible]	34-160	30-202	20-192
GLIAT	mean	252	[illegible]	137	124	157	[illegible]
([illegible]/g/hr)	sem	36	24	16	16	18	18
	range	97-637	56-411	[illegible]-227	44-240	25-229	29-208
GLYCEROL	mean	300	321	287	386	14	403
([illegible]/g/hr)	sem	95	43	[illegible]	120	121	121
	range	64-84	37-[illegible]	43-735	12 1022	16-1094	125-1061

1) 6 males serum triglycerides [illegible] (mean±sem)
8 females serum triglycerides [illegible] (mean±sem)

from one another In this study comprising both male (n=6) and females (n=8) there were several significantly positive correlations Only those that are statistical s gnificant are given in Figure 2 FIAT values from Mc Burney s point correlated with omental FIAT activities r=0 75 p<0 01 The highest correlation was obtained between trochanteric and femoral fat with an r-value of

0 87 p<0 001 There were also several correlations between GLIAT activity at various subcutaneous sites and omental adipose tissue The highest r-value was obtained between GLIAT in epigastric and omental fat r=0 94 p 0 001

Figure 2 Correlations between FIAT values in omental (ome) fat and epigastric (epi) gluteal (glu) femoral (fem) trochanteric (tro) adipose tissue and fat obtained from McBurney s point (MB) The degree of significance is illustrated by —— p< 0 05 ══ p<0 01 ≡ p<0 001



II Clinical studies (papers I III IV and V)

A FIAT, GLIAT and rate of lipolysis in hypertriglyceridaemia

1 A case of severe hypertriglyceridaemia (paper I)

Our interest in the possible role of impaired fatty acid incorporation into adipose tissue (FIAT) was raised by the findings of a normal total post-heparin lipoprotein lipase activity in a patient with type V hypertriglyceridaemia Although this test measures not only adipose tissue lipoprotein lipase activity (see Introduction) it seemed to us at the time of that study that it might be the step after lipoprotein lipase i e FIAT activity which might be impaired and account for the hypertriglyceridaemia in that patient

The macro-method was developed and applied to analyze FIAT and GLIAT in this severely hypertriglyceridaemic patient as well as in controls When the patient was without treatment and his serum triglycerides were about 100 mmol/l which is about 50 times the normal values subcutaneous fat was taken by an open surgical biopsy It was found that his FIAT and GLIAT values were much below the normal range obtained in normolipidaemic controls This patient had previously been treated with nicotinamide for several months and this drug effectively lowered his triglyceride values (24) It was also found that when this drug was withdrawn the serum triglyceride values remained low for several months The possibility was raised that nicotinamide had affected the metabolism of adipose tissue and that this effect might persist for several months These findings also raised the possibility that nicotinic acid might affect some unknown metabolic variables in adipose tissue related to the FIAT-GLIAT process After the first biopsy had been taken we treated the patient with nicotinic acid for three months His serum triglyceride levels were then reduced towards normal values We then repeated the biopsy and found that nicotinic acid had increased both his FIAT and his GLIAT values three to fivefold and that they had been brought into the normal range These findings were taken to indicate that his low FIAT values could account for the hypertriglyceridaemia and that the increased FIAT activity might explain at least in part the triglyceride lowering effect of nicotinic acid

2 Subjects with different types and degrees of hypertriglyceridaemia (papers III and IV)

Our finding of low FIAT in a patient with extreme hypertriglyceridaemia called for further studies to investigate whether FIAT-GLIAT is reduced in any of the more common and moderate types of hypertriglyceridaemia To make such studies possible in a large population a simple and non-traumatizing micro-method was developed (paper II) which also enabled the simultaneous measure-

ment of the rate of lipolysis and of other variables (papers III and IV)

Symptom-free normo- and hyperlipidaemic male and female subjects were investigated FIAT and GLIAT were significantly lower than normal in all types of hypertriglyceridaemia Those with type II A characterized by increased cholesterol values only had values within the normal range FIAT and GLIAT correlated negatively with the serum triglyceride levels in symptom-free males and in females; r-values were close to 0 50 when determined on observations of all subjects Furthermore about 30% of males with type IV hypertriglyceridaemia had FIAT values below the lowest 5% of the controls illustrating that low values are common in hypertriglyceridaemia Figure 3 and 4 summarize the negative correlation between FIAT-GLIAT and the concentration of serum triglycerides

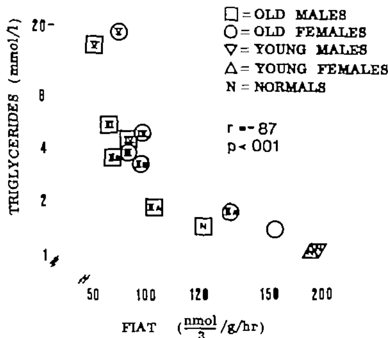


Figure 3 Correlation between FIAT values and serum triglyceride concentrations in young and old male and female subjects with various types of hyperlipidaemia Each symbol represents the mean value of the FIAT activity in one group of subjects The correlation coefficient represents the linear relationship between mean FIAT and mean triglyceride values

Lowest mean FIAT values (Figure 3) were found in those who had the highest serum triglycerides (that is type V) Lowest mean GLIAT values (Figure 4) were found either in type V or type III hypertriglyceridaemia Female subjects usually had higher FIAT and GLIAT mean values than male subjects both in the normal groups and in each type of hyperlipidaemia

Highest FIAT and GLIAT values were found in the young students There was a low degree of correlation (r=-0 26 p 0 02) between age and FIAT in normolipidaemic young and old normolipidaemic male and female subjects Although the age distribution in this study is limited these results may indicate that there is an age dependent decrease in the FIAT process which may be part of the explanation for the known rise in the serum triglycerides with age (33)

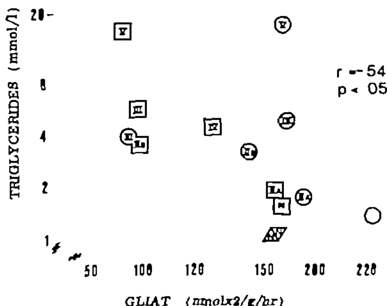


Figure 4 Correlation between GLIAT values and serum triglyceride concentrations in young and old male and female ubjects with various type of hyperlipidaemia Each symbol represents the mean values of the GLIAT activity in one group of subjects The correlation coefficient represents the linear relationship between mean GLIAT and mean triglyceride values Symbols as in Figure 3

The release of glycerol and fatty acids was about the same in all groups of subjects making it less likely that isotopic dilution in the incubation medium can explain these findings These aspects are critically analysed and discussed in papers II and III

There was a close positive correlation between FIAT and GLIAT with r-values around 0 6-0 8 (papers III and IV) suggesting that the generation of -glycerophosphate by newly incorporated glucose may be of importance in the uptake and incorporation of exogenously offered fatty acids at least under the conditions studied

The values for fatty acid and glycerol release were also used to calculate the so called rate of fatty acid retention assuming complete hydrolysis of stored triglycerides as discussed in detail in paper III These values which also indicate the rate of fatty acid removal by adipose tissue were also lower than normal in hypertriglyceridaemic subjects All these findings thus reflect impaired uptake and incorporation into adipose tissue of hypertriglyceridaemic subjects Possible explanations for and interpretations of lower than normal FIAT-GLIAT activities in hypertriglyceridaemia are analyzed and discussed below and in Figures 7 and 8 in the section of General Discussion

B Factors related to FIAT, GLIAT and lipoly is

Several factors in adipose tissue may be related to FIAT-GLIAT and explain at least part of the variation of FIAT-GLIAT in different types of hypertriglyceridaemia Such possible factors were measured and their influence on the negative correlations between serum triglycerides and FIAT-GLIAT was analyzed in papers III and IV

1 Adipose tissue mass and morphology

The amount of calculated body fat was found to be only weakly and inversely (r=- 30 p 05) associated with

FIAT-GLIAT This association was further investigated by determining fat cell size and number (paper IV) since these two variables determine the amount of body fat

We found that fat cell diameter and weight were higher in those with type IV hypertriglyceridaemia When FIAT and GLIAT values were calculated per cell it was found that some groups of hypertriglyceridaemic subjects had lower than normal values; furthermore those with hypertriglyceridaemia had lower than normal FIAT values at one and the same fat cell diameter There was a highly significant positive correlation between FIAT and GLIAT per cell and fat cell diameter in both normo- and hypertriglyceridaemic subjects These findings agree with previous results where other adipose tissue activities were found to be directly related to fat cell size (7 8 10 11 36 71) FIAT and GLIAT was also calculated per cell surface area and found to be lower than normal in hypertriglyceridaemic subjects

The negative correlation between FIAT-GLIAT and serum triglycerides was only insignificantly reduced when the effect of fat cell diameter wa held constant in partial correlation analysis

2 Glucose intolerance

In paper III we discussed the possibility that an impaired glucose tolerance might explain the low FIAT-GLIAT values often found in hypertriglyceridaemia This possibility was investigated and described in paper IV using the intravenous glucose tolerance test There was no correlation between the k-value derived from this test and FIAT-GLIAT or rate of lipolysis The negative correlation between FIAT and serum triglycerides remained unchanged when the influence of the k-value was eliminated by partial correlation analysis These results show that a low FIAT value is not related to impaired glucose tolerance The lack of correlation between the k-value and FIAT GLIAT may be explained by the fact that the k-value is probably determined to a greater extent by the metabolism of glucose in the liver than in adipose tissue

3 Fatty acid spectrum of adipose tissue glycerides

The spectrum of fatty acids in adipose tissue glycerides is related to long term effects of dietary habits (43) and perhaps also to differences in the metabolism of individual fatty acids (34 47 56 73) In paper IV we studied the relation between this spectrum and FIAT-GLIAT as well as the other measured variables The most striking findings were the many correlations between stearic acid and other variables There was a negative correlation between the content of stearic acid and serum triglycerides and body fat as well as fat cell size However the concentration of this acid related positively with the FIAT process The findings suggest that there may be a defect in the metabolism of stearic acid in hypertriglyceridaemia Further studies on the FIAT process should therefore be performed with the use of other labelled fatty acids to investigate possible differences in metabolism of the individual fatty acids in various types of hyperlipidaemia

There were also correlations between other fatty acids and fat cell size and the amount of body fat as well as the serum triglyceride level For instance linolenic and arachidonic acids correlated positively with the k-value of the glucose tolerance test but correlated negatively with serum triglycerides These results have also been reported separately (27)

4 Partial correlation and multiple stepwise regression analysis

Since there were so many interrelations between different factors it is difficult to say which one determines the other The nfluence of each factor on the correlation between FIAT and serum triglycerides was tested in partial correlation analysis It was found that this negative correlation still existed whether one or several of these variables were eliminated in this statistical test

The several correlations between various adipose

tissue variables as well as their correlations with the serum triglyceride concentration suggest that several characteristics in adipose tissue are involved in the control of the serum triglyceride concentration It is however not known if these correlation coefficients represent cause and effect of metabolism or if they just reflect a common variation with some specific variable These aspects were tested in multiple stepwise regression analysis because we wanted to know which variables independently of one another contributed most to the correlation with serum triglyceride concentration which was kept as the dependent variable The highest multiple correlation was obtained by combining the adipose tissue content of linolenic and stearic acid with the FIAT activity per gram The multiple R-value was 0 76 (p 0 001) No additional information was obtained by including other variables in this equation This means that these three variables together may explain 57% (R^2=0 57) of the variation in the serum triglyceride concentration The result illustrate that these three different variables independently of each other express characteristics in adipose tissue of importance in controlling the serum triglyceride concentration Other variables such as the rate of hepatic synthesis and release of triglycerides and the activity of lipoprotein lipase most likely explain the rest of the variation These aspects are further discus ed in the General Discussion

5 FIAT and rate of basal lipolysis

Rate of basal lipolysis may be one important factor determining the FIAT process However we did not find any major difference in glycerol release or in fatty acid release in the various groups of subjects with different types of hypertriglyceridaemia These findings as well as the results from the partial correlation and multiple stepwise regression analysis suggest that other variables are more important in explaining why FIAT is lower than normal in hypertriglyceridaemia in these subjects

Although the rate of basal lipolysis was similar in the subjects of this study it is possible that in other subjects the rate of lipolysis is important in determining the rate of FIAT-GLIAT Thus we *found in a group of hyper*triglyceridaemic and diabetic subjects most of whom were treated with oral antidiabetic drugs that the rate of basal lipolysis was increased and the FIAT process was decreased These results are summarized in Figure 5 The findings are similar to those reported by Östman (79) He also found an increased rate of basal lipolysis and a decreased assimilation of fatty acids using a slightly different method from the one described in this study The possible relationship between rate of lipolysis and the FIAT process in other conditions is presented below

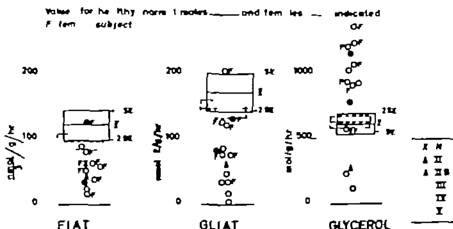


Figure 5 FIAT GLIAT and glycerol release in diabetic patients with different types of hyperlipidaemia Two female type V hypertriglyceridaemic subjects were on insulin the others were treated with oral antidiabetic drugs Corrected FIAT values were calculated and compared with the mean value $\pm$ 2 standard errors of the mean obtained in normal male and female subjects as indicated by the different symbols

6 FIAT and adipose tissue lipoprotein lipase activity

So far we have only measured these two processes simultaneously in one subject who had a severe type V hypertriglyceridaemia (28) Repeated simultaneous measurements were performed when he was treated either with a diet rich in polyunsaturated fatty acids and low in calories or diet and nicotinic acid During this treatment which lasted for about seven months there was a direct correlation between FIAT and lipoprotein lipase activity (Figure 6) irrespectively of treatment given The possible relationship between the FIAT process and lipoprotein lipase activity is further discussed in the section of General Discussion

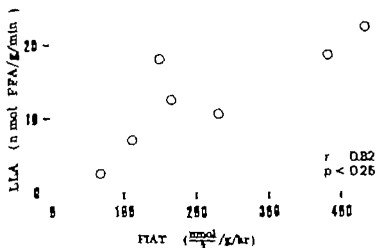


Figure 6 Relation between FIAT activity and lipoprotein lipase activity (LLA) in a case with severe type V hypertriglyceridaemia The lipoprotein lipase assay was kindly performed by Dr Hans Lithell Adipose ti sue was incubated in a 2 1 M glycine NaOH buffer pH 8 6 ionic strength 0 08 containing heparin and C^{14}-labelled triolein in soya bean oil The release of free fatty acids to the incubation medium is taken to indicate the activity of lipoprotein lipase

III Experimental studies

A Effects on FIAT and GLIAT of fatty acid concentration in the medium

When serum triglycerides are hydrolyzed by lipoprotein lipase increasing amounts of fatty acids are offered to the fat cells In such conditions it is very likely that the uptake and incorporation of fatty acids is increased but it is not known to what extent these fatty acids are incorporated into fat cell glycerides This question was examined with our in vitro system as described in papers II and IV where the effects of increasing fatty acid concentration in the incubation medium on FIAT-GLIAT and the rate of lipolysis were studied A physiological spectrum of increasing amounts of fatty acids and labelled palmitic acid was complexed with albumin Adipose tissue from each patient was incubated by the routine procedure at different fatty acid concentrations All the patients in this study were normolipidaemic Glucose concentration in the medium was always 0 1% It was found that FIAT increased linearly with increasing concentrations of fatty acids from about 500 to about 1300 nmol/ml roughly corresponding to a fatty acid/albumin ratio of 1 5-4 5 Fractional FIAT was found to be constant with increasing concentrations of fatty acid Similar results were obtained for subcutaneous and omental fat with higher activities in omental adipose tissue GLIAT in subcutaneous and omental fat also increased as the fatty acid concentration increased There was a highly significant direct relationship in both regions of fat between FIAT and GLIAT activity The rate of lipolysis however was not changed in these experiments

B Relation between rate of lipolysis and FIAT-GLIAT

It is well-known from various studies that when fat mobilizing lipolysis is stimulated in adipose tissue there is a concomitant increase in the reesterification rate of fatty acids (9 11 74 75 76) In human fat however the rela-

tive rate of increase in the esterification of endogenous and exogenous fatty acids is not known Our studies in paper VI were designed to elucidate the relation between rate of lipolysis and rate of incorporation of exogenous fatty acids and glucose

We investigated the influence of increases lipolysis on FIAT by using either isoproterenol a β-agonist or theophylline a phosphodiesterase inhibitor (for review 53) Various concentrations of isoproterenol were added in vitro to fat obtained from each patient The increase in lipolysis was directly related to the dose of of isoproterenol Corrected FIAT values were found to be about 30-40% lower than in the basal state at the highest concentrations of isoproterenol They were inversely correlated with the basal activity which suggests that the increased rate of lipolysis decreased the incorporation of exogenous fatty acids considerably Comparable results were obtained with theophylline

Nicotinic acid and Prostaglandin E_1 (PGE_1) decreased the basal rate of glycerol and fatty acid release (5 22 53) and stimulated FIAT by about 30% The results with PGE_1 are interesting since this hormone is synthezised in fat (67) and may participate in the regulation of FIAT and the rate of lipolysis

Isoproterenol stimulated glucose incorporation (GLIAT) indicating that exogenous glucose was used for the synthesis of α-glycerophosphate to maintain the esterification of incorporated endogenous fatty acids However GLIAT was not affected by the other agents This absence of effect of nicotinic acid and PGE_1 on GLIAT may be explained by the fact that different endogenous metabolites may be formed and used in the esterification process

It may be argued that the continuous increase in the medium fatty acid concentrations when the rate of lipolysis is increased gives rise to a higher ratio of fatty acids to albumin a situation resembling the addition of fatty acid in vitro described above We therefore recalculated our FIAT activities as fractional FIAT We found that there was a highly significant inverse rela-

tionship between the change in rate of lipolysis and the change in the FIAT process irrespectively of the agent stimulating or inhibiting the rate of lipolysis These results and possible intracellular effects are summarized in Figure 7 and discussed in the section of General Discussion

GENERAL DISCUSSION

I FIAT values

The main finding in the present studies was a FIAT activity which was lower than normal in subjects with hypertriglyceridaemia These results were obtained not only in severe hypertriglyceridaemic subjects but also in those with moderate degrees of different types of hypertriglyceridaemia Furthermore low FIAT values were common In the male hypertriglyceridaemic population 36% had values for fatty acid incorporation below the 5th percentile of the normolipidaemic group and 15% had values below the lowest normal value There was also a negative correlation between FIAT activity and levels of serum triglycerides Similar results were obtained if FIAT values were expressed per fat cell surface area or per fat cell

FIAT activities in fat from the abdominal wall at McBurney s point is qualitatively representative of body fat as a whole This is shown by the fact that subcutaneous fat from different sites has closely similar values under the various circumstances in which it was examined and that omental fat although quantitatively more active increases and decreases its FIAT activity in parallel with subcutaneous fat However values from McBurney s point cannot be used to calculate total body fat activity since we do not know the different proportions of subcutaneous and omental adipose tissue nor can we assess variation in blood flow and neurogenic activity at different morphological sites which occur in vivo

II GLIAT values

We also found that GLIAT was lower than normal in hypertriglyceridaemic subjects and negatively correlated

with serum triglycerides The correlation between FIAT and GLIAT was about r=0 6-0 8 GLIAT values behaved in the same way as FIAT values at different subcutaneous sites and omental fat These findings indicate that there is a close relationship between the incorporation of exogenous glucose and its conversion to α-glycerophosphate and the incorporation of exogenous fatty acids in the fasted state

III Factors related to FIAT and GLIAT

There may be several factors contributing to the existence of low FIAT-GLIAT values in hypertriglyceridaemia Such variables are the amount of body fat fat cell diameter and fat cell surface area and the stearic and perhaps also the linolenic acid content of adipose tissue However neither the total calculated fat cell number nor the k-value of the intravenous glucose tolerance test were related to FIAT or GLIAT Using partial correlation analysis and keeping the various factors constant the significant inverse correlation between FIAT and GLIAT activity and the concentration of serum triglycerides persisted

A Intracellular metabolism of fatty acids

The findings indicate that there are factors other than those presented above to account for the low FIAT-GLIAT values in hypertriglyceridaemia There may be differences between normo- and hypertriglyceridaemic subjects in their intracellular metabolism of fatty acids and glucose which may explain why lower than normal amounts of fatty acids and glucose are incorporated into di- and triglycerides in hypertriglyceridaemia Such possible differences in the intracellular metabolism are summarized schematically in Figure 7

It is possible that hypertriglyceridaemic subjects do not incorporate all extracellularly offered fatty acids perhaps due to a defect in their membrane transport mechanism (56 73) or although they incorporate fatty acids properly only a few of them reach the intracellular pool involved in esterification This last hypothesis is supported by finding that those who have low FIAT values have a proportionally higher percentage content of incorporated ^3H-activity in their free fatty acid pool than in their glycerides These incorporated but unesterified fatty acids may accumulate separately in other compartments (Figure 7) where they may influence other adipocyte activities such as the early stages involved in glucose uptake and its subsequent metabolism (34)

B <u>Local extracellular concentration of fatty acids</u>

Only a small proportion of circulating free fatty acids is incorporated into adipose tissue when labelled free fatty acids are infused intravenously (56) This may be because the extracellular concentration is too low to influence the FIAT process significantly The fatty acids that are incorporated into adipose tissue are almost exclusively derived from circulating triglycerides by the action of lipoprotein lipase In this metabolic step high local concentrations of fatty acids are created at the capillary wall This concentration is partly determined by the concentration of circulating triglyceride-fatty acids and partly by the activity of lipoprotein lipase If it is valid to extrapolate our in vitro data to in vivo conditions our findings of increased FIAT process in relation to raised extracellular concentrations of fatty acids would indicate that there is a constant fractional removal rate at least in normotriglyceridaemic subjects If the lipoprotein lipase activity is normal in hypertriglyceridaemic subjects then the increased substrate concentration (circulating triglycerides) would give rise to an increased local concentration of fatty acids which might overcome a low FIAT process and permit

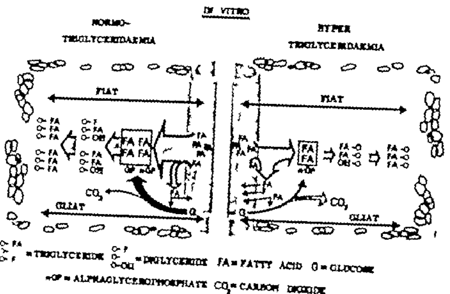


Figure 7 A schematic drawing illustrating the FIAT and GLIAT process in normo- and hypertriglyceridaemic subjects The figure indicates possible alternative pathways of metabolism The dotted lines symbolize possible compartmentalisation and theoretical routes for incorporated fatty acids and glucose and their inter-relations The different symbols are explained in the Figure The interpretation of these results and theoretical speculations are given in the section of Results or in the General Discussion

triglyceride-fatty acids to be incorporated into adipose tissue glycerides However this hypothesis is only valid if also hypertriglyceridaemic subjects increase their FIAT capacity when the concentration of fatty acids increase i e that their fractional FIAT is constant If this conditions exists in vivo it would explain why hypertriglyceridaemic subjects are obese rather than lean

These speculations rest on the assumption that a low FIAT activity is the primary defect in hypertriglyceridaemia It is however equally well possible that impairment of the FIAT process does not develop until the adipose tissue mass is enlarged to a critical stage (genetically determined?) Not until then a defective FIAT process may develop perhaps because fractional removal rate of exogenous fatty acids does not increase in parallel with increasing fatty acid concentrations Such an impairment might be due to a block in the intracellular esterification process as discussed above This process of fatty acid incorporation may furthermore in certain conditions be intimatly related to the rate of lipolysis as commented below

C Intracellular metabolism of glucose

Our finding of a lower than normal GLIAT process in hypertriglyceridaemia (Figure 4 7) suggest that at a given fatty acid concentration less α-glycerophosphate is formed than in normotriglyceridaemia This also indicates that there is little substrate for esterification of fatty acids Whether this low GLIAT activity is a primary cause of the low fatty acid incorporation in hypertriglyceridaemic subjects is currently not known However it should be pointed out that when exogenous concentrations of fatty acids increase there is a concomitant increase in the GLIAT process showing that the fatty acid concentration increase the rate of exogenous glucose incorporation into adipose tissue glycerides It is however not known whether increasing concentrations of fatty acids in hyper-

triglyceridaemic subjects also stimulate the incorporation of exogenous glucose It is possible that in hypertriglyceridaemic subjects glucose is converted to other metabolites such as CO_2 or that they use endogenous substrates formed by glycolysis or via the glyceroneogenetic pathway (34 66 75) rather than exogenous glucose for esterification If these pathways are more active in hypertriglyceridaemic subjects this could be one explanation for their low GLIAT values

IV Relations between the rate of lipolysis and the FIAT-GLIAT process

A Unstimulated lipolysis

In this discussion we have o far left out the role of lipolysis in the intracellular metabolism This process can influence and regulate the flow of exogenous fatty acids and glucose in several ways In our clinical material however the basal rate of lipolysis was not increased in any of the group of hypertriglyceridaemic subjects Furthermore there wa no change in the statistical degree of correlation between FIAT-GLIAT and serum triglycerides when the rate of ba al lipolysis was kept constant in partial correlation analysis These findings make it rather unlikely that our low FIAT values can be explained on the basis of an increased rate of lipolysis There may however be partial hydrolysis of stored glycerides (3 11 74) which could account to a small degree for the low FIAT values in hypertriglyceridaemia Our findings of very low FIAT activities in diabetic hypertriglyceridaemic subjects however may well be due to their increased rate of basal lipolysis

B Stimulated lipolysis

1 In vitro studies

In certain conditions in vivo such as stress and exercise the rate of fat mobilizing lipolysis in adipo e

tissue is increased and may influence the FIAT process Such situations were mimicked in our in vitro system Our results with various agents stimulating and inhibiting lipolysis indicate that an increased rate of lipolysis is a major determinant of the rate of the FIAT process In these studies we always found an inverse relationship between rate of lipolysis and the FIAT process whatever the mode of action of agents which caused stimulation or inhibition of lipolysis Based upon these findings we summarize the influence of lipolysis on the FIAT process and its possible influence on other intracellular events related to the lipolytic chain and the FIAT process (Figure 8)

When lipolysis increases there is an increased release of glycerol and fatty acids to the extracellular compartment It is also likely that the intracellular concentration of fatty acids increases (11 30 74 75 76) in one or several compartments (30 50 56 74 75 76) and some of these fatty acids drain into the active compartment engaged in in esterification The turnover rate of intracellular fatty acids may also be increased since it is known that when the rate of lipolysis is increased the rate of re-esterification of fatty acids also increases (11 74 75 76) It is likely that part of this increase is due to esterification of endogenously derived fatty acids Endogenous and exogenous fatty acids may distribute in different pools and endogenous fatty acids may be more readily available for esterification explaining why FIAT values are decreased when rate of lipolysis is increased On the other hand if exogenous and endogenous fatty acids distribute in the same pool there would be dilution of this pool which may make it more difficult for exogenous fatty acids to reach esterification sites (74 75 76) When the rate of lipolysis is high there is reduced availability of ATP (49) and this may also contribute to low FIAT values since ATP is needed in the esterification process (11 34 49 75)

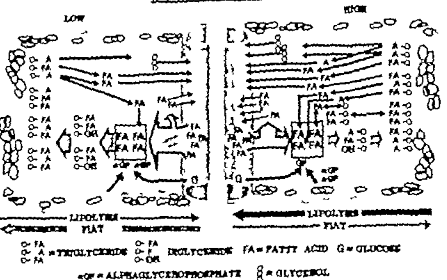


Figure 8 A schematical illustration of the inverse relationship between fat mobilizing lipolysis and the FIAT process The Figure summarizes our results and indicates possible explanations for lower FIAT activities in conditions where lipolysis is stimulated Results and explanations are given in the section of Results or in the General Discussion The symbols are explained in the Figure

When the rate of lipolysis is high a greater than normal amount of partial glycerides is formed (3) They may also be involved in the esterification process and may explain why there in some conditions is no increase in the incorporation of exogenous glucose (GLIAT) when lipolysis is stimulated

2 Possible implications in vivo of our in vitro findings

The inverse relationship between the rate of lipolysis and the FIAT process may explain the rise in serum triglyceride concentrations on the basis of two different mechanisms

Firstly free fatty acids are liberated from adipose tissue and can be used as substrate in the energy metabolism of muscles or as substrate in the hepatic synthesis of triglycerides When the rate of lipolysis is high and the supply of fatty acids to the liver exceeds the amount oxidized it will give rise to an increased synthesis of triglycerides in the liver and to their release into the blood stream

Secondly when the rate of lipolysis is high lipoprotein lipase may be inhibited (58) This together with a decrease in the FIAT process contributes to the decrease in the removal rate of circulating triglyceride-fatty acids The total net effect will then be a rise in the serum triglyceride concentration However when the rate of lipolysis is low or inhibited by drugs such as nicotinic acid lipoprotein lipase activity and the FIAT process are stimulated and the removal rate of triglyceride-fatty acids is increased Such a direct relationship between lipoprotein lipase and the FIAT activity may exist in vivo and is suggested by our observations in a severe hypertriglyceridaemic subject treated with diet and nicotinic acid Although we did not measure adipose tissue lipoprotein lipase activity during treatment of our severe hypertriglyceridaemic patient presented in paper I it is possible that this treatment stimulated the

lipoprotein lipase activity as well as the increase in the FIAT process It is also possible that nicotinic acid inhibited rate of lipolysis in this patient In future studies these factors must be determined simultaneously to know which is the most important one in the control of triglyceride-fatty acid removal and to learn on which process lipid lowering drugs and regimes are active

V The role of a low FIAT process in different types of hypertriglyceridaemia

Our studies of the possible role of a low FIAT process as a rate limiting step in the removal of triglyceride-fatty acids have all been performed in the fasting state In the fed state the intake of lipids and carbohydrates increases triglyceride synthesis and release from the liver In such conditions those with low FIAT values are very sensitive to excess synthesis of triglycerides by the liver When the rate of synthesis is increased for long periods of time even those who have only minor disturbances in their FIAT process may develop hypertriglyceridaemia Our findings of reduced FIAT activity in all types of hypertriglyceridaemia may be taken to indicate that this is a general occurrence and that the characteristics by which the different types of hyperlipidaemia are distinguished from one another are determined by other processes

We do not know at present whether a low FIAT activity is part of the explanation for the development of hypertriglyceridaemia or whether it is itself caused by the hypertriglyceridaemia We know however that acute elevations of serum triglyceride levels by infusions of exogenous triglycerides (Intralipid^R) (77) do not further decrease the FIAT activity The results from that study also indicate that the FIAT process may be operating in vivo since there was a positive correlation between removal rate of circulating triglycerides and the FIAT activity

VI Conclusion

The process of fatty acid incorporation may be one of the general mechanisms controlling the balance between uptake of circulating triglyceride-fatty acids and release of stored triglyceride-fatty acids in various conditions Our finding of an impaired FIAT process with a normal rate of basal lipolysis in hypertriglyceridaemic subjects suggests that the primary defect is in the FIAT process and that it contributes to the reduced removal of circulating triglyceride-fatty acids from blood to adipose tissue This hypothesis needs to be verified by in vivo studies before the role of the FIAT process in the control of removal of triglyceride-fatty acids from blood to adipose tissue is established

GENERAL SUMMARY

1 Methodological clinical and experimental studies were performed on the fatty acid (FIAT) and glucose (GLIAT) incorporation into adipose tissue in relation to hypertriglyceridaemia

2 Methods were developed for determination of FIAT and GLIAT and rate of glycerol release from small amounts (about 30 mg) of human adipose tissue obtained by needle biopsy

3 FIAT and GLIAT were found to be lower than normal in extreme hypertriglyceridaemia (type V) and in all types of moderate hypertriglyceridaemia (that is type II B III and IV)

4 FIAT and GLIAT correlated positively

5 There was a h ghly significant negative correlation between FIAT and GLIAT on one hand and serum triglyceride concentrations on the other hand

6 Lipolysis rate was the same in all except the diabetic hypertriglyceridaemic subjects who had increased rate of lipolysis

7 FIAT and GLIAT activities were of similar magnitude in different subcutaneous regions but about 50% higher in omental than in subcutaneous fat FIAT and GLIAT were very closely related both in subcutaneous fat and in omental adipose tissue

8 FIAT and GLIAT in subcutaneous and omental fat from normotriglyceridaemic subjects was directly related to the extracellular fatty acid concentration

9 FIAT and GLIAT per fat cell increased with fat cell size

10 There was a positive correlation between stearic acid content in adipose tissue glycerides and FIAT activity

11 There was no correlation between FIAT and GLIAT and the k-value of the intravenous glucose tolerance test

12 Although fat cell diameter and fat cell surface area as well as the content of various fatty acids in the extracted glycerides were correlated with FIAT per gram the negative correlation between FIAT-GLIAT and serum triglycerides remained significant when all these variables were held constant in partial correlation analysis These results suggest that there must be other factors in the fat of hypertriglyceridaemic subjects to account for their low FIAT and GLIAT values Such possible intracellular differences in the metabolism of fatty acids and glucose were discussed

13 It was possible to predict 57% of the serum triglyceride variation by combining values for FIAT per gram with the content of stearic and linolenic acid in adipose tissue These results illustrate that these three variables independently of each other express characteristics in adipose tissue of importance in controlling the serum triglyceride concentration

14 There was a negative correlation between rate of lipolysis and FIAT activity when lipolysis was stimulated by isoproterenol or theophylline or inhibited by nicotinic acid or Prostaglandin E_1 These findings suggest that the rate of lipolysis in certain conditions is a major determinant of the FIAT process

CONCLUSION: Lipoprotein lipase liberates fatty acids from serum triglycerides We have measured the rate of uptake and incorporation of fatty acids into adipose tissue glycerides (FIAT) and conclude that it is an important factor in determining the serum triglyceride level A low FIAT activity may contribute to the occurrence of hypertriglyceridaemia

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Effects of Acute Infectious Disease on Circulatory Function

By Göran Friman

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University Hospital, Uppsala, Sweden

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Uppsala 1976

Länstryckeriet Nyköping
1976

CONTENTS

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Chapter 1
INTRODUCTION

Several studies of circulatory function during acute infectious disease have dealt with peripheral circulation or shock (Stead & Ebert 1940; Ebert & Stead 1941; Fine 1953; Burch *et al.* 1961), and others specifically with blood volume (for review see Gilbert 1960). Further, myocarditis, suggestive or manifest, appearing in the course of acute infectious disease has been the subject of a number of circulatory studies (Bengtsson 1957 C; Levander-Lindgren 1965; Bengtsson & Lamberger 1966; Bergström *et al.* 1970; Gerzén *et al.* 1972).

Bengtsson (1957 D) in his extensive studies of patients showing ECG abnormalities during acute infectious diseases also investigated a group of convalescent patients after such illnesses in whom ECG abnormalities were not found (Bengtsson 1956). Further Berven (1962) studied cardiopulmonary function in the post-infectious phase of "atypical" pneumonia, and included 12 patients convalescing from other acute infections as the control group. More specifically acute viral hepatitis has been the subject of several studies with different aims (Edlund 1971; Lundbergh 1974).

Even without cardiac involvement symptoms of lassitude and debility are often encountered in the immediate post-febrile course of acute infections (Stuart-Harris 1965). The factors contributing to these symptoms may be manifold. However, a disturbance of circulatory function seems likely in several cases, since symptoms more clearly related to the cardiovascular system may develop (Lyon 1952). Such symptoms are often indistinguishable from those of neurocirculatory asthenia (Lyon 1952).

Since epidemiological patterns change and since data have accumulated in recent years on the deleterious effects of bed rest, it was felt to be of interest to perform a prospective investigation of acute febrile infections without cardiac complications to try to establish the extent and duration of physical deterioration caused by these illnesses, attempting to discriminate between the effects of bed rest and those of the illness as such. An additional aim was to investigate possible late complications in these illnesses.

Since no comparable bed rest study was found in the literature a control group subjected to clinical bed rest was investigated. The complete results of that study will be presented separately (Friman 1976 B).

Besides the effects of the selection criteria the final composition of the study group, irrespective of its size is mainly determined by two factors: firstly the epidemiological pattern in the population served by the hospital during the period of the investigation, and secondly the fact that only hospitalized patients were used. This implies that the study group represented the most intense or

Table II Diagnoses and aetiologies of patients with acute infectious diseases in different series.

			Series				
Diagnosis No.	Diagnoses and aetiologies	No. of patients	M1 (N)	M2 (N)	M (N)	F (N)	M + F (N)
	Various viroses	25					
1	Influenza, type A		1		1	2	3
2	Measles					1	1
3	Infectious mononucleosis		6		6	2	8
4	Cytomegalovirus		1	1	2		2
5	Hepatitis B		3		3		3
6	Hepatitis A		1	1	2	1	3
7	Mumps (without meningoencephalitis)		1	1	2		2
8	Agent not established		1		1	2	3
	Serous meningoencephalitis	26					
9	Mumps (with or without other complications)		9	2	11	1	12
10	Tick-borne encephalitis (TBE)		1		1		1
11—14	Echovirus 3 6 14 18 (one of each)			1	1	3	4
15—17	Coxsackievirus A9 B3 B4 (one of each)					3	3
18	Coxsackievirus B2			1	1	1	2
19	Mycoplasma pneumoniae		1		1		1
20	Agent not established		1	2	3		3
	Pneumonia	16					
21	Mycoplasma pneumoniae		3	3	6	7	13
22	Measles + Mycoplasma pneumoniae		1		1		1
23	Bacterial aetiology		1		1	1	2
24	**Mycoplasma pneumoniae** (no pneumonia, no meningoencephalitis)	1				1	1
	Bacterial infections (except pneumonias)	11					
25	Tonsillitis or peritonsillitis		4		4	4	8
26	Cervical lymphadenitis					3	3
	Virosis with bacterial complication	1					
27	Influenza + sinusitis					1	1
	No. of patients	80	35	12	47	33	80

complicated cases of the illnesses prevalent in the community during the period of the investigation. For practical reasons, by no means all patients admitted during the time period, filling the above mentioned criteria, could be included in the study Despite this, the present study group can be considered representative of patients in hospital with the diagnoses under study since very few refused to participate.

The illness was considered to start at the onset of the first symptoms and to be over when fever had abated, fever being defined as a rectal temperature of at least 37.5 C in the morning or 38.0 C in the afternoon. In the cases with hepatitis, in whom fever was lacking or of short duration, the disease was still active at the time of the first measurements (see chapt. 3). However in no case was the serum aspartate-aminotransferase (S-ASAT) or alanine-aminotransferase (S-ALAT) above 6.0 μ/l or the serum bilirubin above 45 mg/l, so an exercise test was not considered deleterious and 1971). The duration of the illness at the time of the first measurements was used in the calculations for these cases.

Data on duration of illness, fever and bed rest, are shown in Table III. Equivalent data for different subgroups of the series are included in Table XII, namely subgroups VM (= viral + mycoplasma infections, aetiological diagnoses 01—22, 24 and 27 in Table II) B (= bacterial infections, Nos. 23 25 and 26), P (= pneumonias, Nos. 21—23) and ME (= meningo-encephalitis, Nos. 09—20). The number of days with symptoms, fever and bed rest before admission to hospital were estimated by direct questioning and are included in the figures of Table III

Control group. Twenty two healthy men, the majority of whom were students, served as control group (series C) (Table I) One of the control subjects suffered mild bronchial asthma which was quiescent during the period of the investigation except on the third occasion of measurements (see chapt. 3) These results were therefore partly excluded from the calculations The control subjects were confined to bed, one at a time for seven days (Table III) in a special room on a ward, the aim being to achieve the same degree of physical activity (clinical bed rest) and energy intake as encountered by the patients and described under Clinical procedure.

Table III Durations of illness (DI), of fever (DF), and of bed rest (DB) for different series of patients and for control subjects. AD = all diagnoses.

		DI		DF		DB	
	N	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Total series (AD)							
M1	35	10.8 NS	6.5	8.0 NS	4.9	8.5 NS	4 0
M2	12	10.5	5 6	7 7	5.0	8.1 NS	5 1
C	22	—	—	—	—	7 0 NS	0 0
M	47	10 7 NS	6.2	7 9 NS	4 9	8 4	4.2
F	33	8.1	5 6	6.5	4 1	6.5	4 0
M + F	80	9.6	6.1	7 4	4 6	7 6	4.2

Clinical procedure and Findings

All subjects, patients and controls, were examined by the author The routine admission procedure for patients with acute infectious disease was followed including a history a complete physical examination, haemoglobin assay (B-Hb), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, differential count, and urinalysis for albumin, glucose, and cells. One serum sample was drawn and stored at —21°C for later serological tests. No special attention was paid to the symptom of myalgia in the present series, except in seven patients in whom muscle biopsies were also performed, the results of which have been reported separately (Åström et al. 1975 Åström et al. 1976 A B).

Additional investigations, performed on an individual basis, included chest X ray chemical tests of hepatic or pancreatic involvement, lumbar puncture, and electroencephalography (EEG) etc.

The clinical investigations performed revealed in no case unexpected complications to the illness concerned.

On the ward, patients and control subjects were allowed up only for personal hygiene. Meals were eaten sitting up in bed. This regimen was continued for the duration of fever with the patients (according to clinical judgement in the hepatitis cases) and for 7 days with the control subjects. However the latter sat in an armchair for a quarter of an hour twice daily from the 5th day If symptoms permitted, the patients were encouraged to stay out of bed after subsidence of fever and the measurements (see chapt. 3) were performed as soon as possible.

On average, the patients ate less while they had fever because of symptoms of nausea and anorexia. One patient, suffering mumps pancreatitis, received intra enous fluids for 2 days The energy content of the normal hospital diet being 9 21 × 10^6 J per day (21 per cent protein 29 per cent fat, and 50 per cent carbohydrate) was reduced by about 30 per cent during the first two days of bed rest in all but six control subjects, who were on a starvation diet for the first 4 days. After that time, standard hospital meals were given to all th control subjects. Fluid intake was unrestricted in quantity

Acetyl salicylic acid or paracetamol was given to alleviate fever and myalgia, when present. Six of the control subjects were also given this drug in a dosage of 3 grams daily

Different antibiotics, mostly phenoxymethyl penicillin, had been administered to 22 patients at home before admission. On the ward, such drugs were administered to 32 patients. Three patients had been given sulphonamides before admission

After the measurements, the patients were, as a rule, discharged from hospital within a couple of days. The control subjects were discharged immediately The patients returned home for normal convalescence and were seen by the author in the outpatient department, generally —3 weeks later In addition to the routine procedure, which included a physical examination, B-Hb, ESR, and urinalysis for albumin, glucose, and cells, a convalescent serum sample was then drawn for serology The majority of the patients had no residual symptoms. Thirty-one patients reported varying degrees of reduced physical fitness, mostly general tiredness. In five patients, who had suffered meningoencephalitis, headache or dizziness was present. One of the latter cases, a woman with mumps meningoencephalitis, suffered severe headache, fatigue, and hyperacusis but had recovered by the time of the follow-up measurements (occasions II, III, and IV Table IV). Two cases who suffered viral hepatitis reported marked lassitude, and liver function tests were found to be still abnormal, remaining so in one of them on occasion II, but becoming normal by occasion III. B-Hb was within normal limits for sex and age in all cases and ESR was less than 30 mm per hour in all cases but three in whom it subsequently became normal.

Thus, all but three of the patients could recommence work or school, either immediately or after a short prolongation of the sick-leave. All but the three severe cases were clinically well by the time of occasion II, but a minority had then still not resumed work. Two of the three severe cases had recovered at occasion III, while the third patient did not return for follow-up.

Diagnosis

For a diagnosis of meningitis > 6 cells per cm^3 of cerebrospinal fluid was required and a positive chest X-ray was required for a diagnosis of pneumonia.

It was endeavoured to confirm the initial bedside diagnoses by isolation of viruses or bacteria and by serological tests. In several cases extensive work was necessary before a final aetiology was established. These studies were carried out with routine methods at the Departments of Virology and Clinical Bacteriology University of Uppsala and at Statens Bakteriologiska Laboratorium, Stockholm.

Betahaemolytic streptococci were found on culture in only one of eight patients with tonsillitis. Antistreptolysin (AST) tests on paired sera failed to establish this diagnosis in the others. Three cases were complicated by a peritonsillitis. The bacterial nature of the remaining four cases of

tonsillitis was considered probable on clinical grounds (WBC, ESR, and reaction to antibiotic treatment). In the three cases with septic cervical lymphadenitis the diagnosis was similarly based on clinical findings. These patients failed to show titre rises against toxoplasma, listeria, or cytomegalovirus, and the Paul-Bunnell test was negative. The antistaphylolysin (ASta) titres were low However in one of these patients finger and toe tips showed scaling, and in another raised AST titres were encountered to support a streptococcal aetiology

Attempts at virus isolation from faeces or cerebrospinal fluid were made in some of the patients with serous meningitis and were successful in two cases having echovirus 6 and 18 meningitis. Immunodiffusion tests for hepatitis B antigen (Hb_sAg) were performed in all cases with viral hepatitis, being positive in only one of three narcotic addicts. One of the other two addicts had been treated for HB_sAg-positive hepatitis 6 months previously The current illness was interpreted as a recrudescence due to a new bout of addiction, or activation due to development of chronic aggressive hepatitis, signs of which were found on liver biopsy In two of the three cases suspected of suffering hepatitis A, other members of the families had recently fallen ill with the same disease. The third case was sporadic and not consistent with infection with Epstein-Barr virus or cytomegalovirus, and the HB_sAg-negative specimen was sampled as early as 5 days after the onset of jaundice.

In all but 12 cases with viral or mycoplasma infections (six of whom were the cases with iral hepatitis), the diagnoses were established by serological tests on paired sera. A fourfold or higher rise in titre from acute to convalescent serum was required, or a fourfold decrease in titre or in some cases, only high antibody titres.

Thus, complement-fixing (CF) antibody tests were used in the cases with diagnoses Nos. 1 2, 4 7 9 19 21 22, -4 and ?7 in Table II. Three cases with diagnosis No. 1 and the cases with diagnoses Nos. 2- and 19 failed to show a titre rise. However high titres of antibodies against Mycoplasma pneumoniae (M.p.) were found in the first serum of the pair (512, 32, 32, 1280 and 128 respectively), and these levels were accepted as diagnostic (first serum obtained on the 7th—19th days after onset of illness) in combination with chest X-ray findings and response to antibiotic therapy In the case with diagnosis No. 24 a titre of 40 was recorded in both sera. However the diagnosis was considered probable since there was an epidemiological connection with the case with diagnosis No. 19 In both these cases the disc neutralization test described below proved negative. In the two cases with diagnosis No. 7 and in two cases with diagnosis No. 9 moderately high titres of antibodies against mumps virus were found in the first serum (64 16 16, and 16, respectively) and in combination with epidemiological data and findings of parotide swelling, or chitis, or pancreatitis these were accepted as diagnostic (first serum obtained on the 7th—9th days after onset of illness). In the two cases with diagnosis No 4 CF antibody titres of 64 to cytomegalovirus were found in the first serum, in combination with occurrence of atypical lymphocytes in the blood, abnormal liver function tests, and negative Paul-Bunnell tests. Since significantly lower titres were recorded in sera sampled 3.5—4 months later these levels were accepted as diagnostic, although these first sera were obtained as early as on the 21st and 17th days of the illness. Finally in the patient with diagnosis No 22, who presented with a typical measles exanthema, a high CF antibody titre of 160 to measles virus was found in the first serum obtained on the 16th day after the onset of the illness and was therefore accepted as diagnostic.

Haemagglutinin inhibiting (HI) antibodies were found in the serum pair of the case with diagnosis No 10 in titres of 40 and 80 which were accepted as diagnostic (first serum obtained on the 20th day after onset of illness) since the patient had meningoencephalitis and came from an area in which ticks are known to be prevalent.

A disc neutralization test (NT) for antibodies against enteroviruses (Lagercrantz *et al.* 1973) established the aetiology in the cases with diagnoses Nos. 11—18 This test, covering 18 enteroviruses, was also applied in the cases with diagnoses Nos. 8 and 20 but the results were negative. CF tests

against influenza virus A and B Chlamydia psittaci, adenovirus, M.p., parainfluenza viruses 1 2, and 3 and respiratory syncytial virus were carried out in the cases with diagnoses Nos. 8 and 23 and CF tests against mumps and herpes simplex viruses, and M.p. in the cases with diagnosis No. 20 all being negative.

In the cases with diagnosis No. 3 presenting with tonsillitis, atypical lymphocytes in their differential counts, or abnormal liver function tests, the Paul-Bunnell-Davidsohn test was positive in single serum.

Chapter 3
GENERAL PROCEDURE AND METHODS

Procedure

In all series of subjects, M F and C (chapt. 2) measurements were made on three comparable occasions (Table IV): as soon as possible after the illness/bed rest period (occasion I) about 1 month later (occasion II) and about 3¹/ months later (occasion III) In addition, control measurements were made after about one year (occasion IV) in series M and F and one week prior to bed rest (occasion 0) in series C.

..ne choice of intervals between the measure was influenced by the following conside-ns. Firstly it is known from clinical practice at patients with the illnesses under study as a rule have passed the period of convalescence and resumed work one month after discharge However in a previous study of acute infections in hospitalized patients (Bengtsson 1956) the level of physical working capacity of the patients had not quite reached that of a control group by that time. Therefore in the present study measurements were made on a third occasion, after about three months, to determine the habitual level of function of the individual patients and for use as reference level. In order to minimize the possibility of a training effect, certain measures were taken. Thus, the patients were carefully told to resume their individual habits of daily life and physical activity as soon as possible after the consultation at the out patient department and to keep this level, if possible, until occasion III. Further they were not informed that measurements were planned on a fourth occasion after about one year These measurements were justified by the twofold aim of firstly establishing possible clinical sequelae and secondly — since such sequelae were not apparent — ensuring that the measurements performed on occasion III were representative for the individual's usual level of function.

Throughout the period of the study the investigation was extended by including additional measurements, so that the numbers of patients subjected to different measurements varied appreciably Thus, during the first 6 months of the study exercise tests (chapt. 6) and orthostatic tests (chapt. 7) were carried out only on two occasions (occasions I and II) and measurements of heart volume (chapt. 5) and lactate concentration (chapt. 9) were not made. Further measurements of respiratory gas exchange (chapt. 8) were not performed until the last year of the investigation. The fact that the majority of the subjects were patients, who took part in the investigation voluntarily contributed to the variability to a minor extent, since it was not always possible to make all measurements on every occasion. Some patients suffered mild febrile infection during the first three months after the initial illness. In those cases the measurements were postponed to give a free interval of one or three months, respectively However this was not always possible and on three occasions the measurements were therefore omitted in the calculations. In the control group, measurements were omitted only on one occasion although not in all variables, since the subject suffered asthmatic symptoms during exercise Common colds without fever were disregarded.

Methods

ECG. Electrocardiograms were recorded on an ink jet, 4 channel Mingograph EM 34 (Elema Schönander Stockholm) being calibrated so that 10 mm corresponded to 1 mV and with a paper speed of 50 mm per second for evaluation of the ST interval and T wave and of 10 mm per second for detection of arrhythmia and for counting the heart rate At rest and during orthostasis leads

Table IV Time (days) from end of illness/bed rest until occasions (I, II, III and IV/0) of measurements. Occasions IV/0 refer to control measurements, 0 for series C (prior to bed rest), IV for other series (1 year after illness).

	I			II			III			IV/0		
Series	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N
M	2.0	1.8	47	37.4	7.4	38	111.4	25.8	31	396.0	51.7	27
C	0.0	0.0	22	32.2	6.9	22	101.4	25.8	22	—12.8	2.9	22
F	1.8	2.1	33	41.0	9.3	29	114.0	21.2	28	412.2	58.5	30

I, II, III aVR, aVL, aVF and $V_{1, 2, 4, 5}$ and $_7$ were recorded. During exercise leads CH (H = head)$_{2, 4, 5}$ and $_7$ were recorded instead of V leads.

Heart rate. Heart rates were counted from the ECG (see above).

Blood pressure. Blood pressures were measured indirectly with a calibrated mercury manometer (cuff size 13 × 35 cm) on the right upper arm. At rest, the disappearance of the 5th sound of Korotkow was taken as the diastolic blood pressure level. During exercise, the 4th phase of Korotkow was, if audible, indicated as the diastolic blood pressure but, because indirectly measured diastolic blood pressure recordings during exercise have often proved to be inaccurate (Karlefors *et al.* 1966) these values were omitted in the calculations.

Exercise tests. Exercise tests were performed in the sitting position according to Sjöstrand (1947) and Wahlund (1948) on an electrically braked bicycle ergometer (Elema-Schönander EMT 369) based on the principles described by Holmgren & Mattsson (1954). The ergometer was calibrated regularly during the course of the investigation. The submaximal loads used were, with a few exceptions, multiples of 49.0 watts for series M and C and multiples of 32.7 watts for series F. The pedalling rate was 60 revolutions per minute. The standard working time was 6 minutes on each load. The room temperature varied between 18 and 25 C. A fan was used at the higher temperatures.

Respiration, ventilation, and gas exchange. Respiratory rates were measured at rest by inspection of the thoracic movements, and during exercise by auscultation over the trachea.

The peak expiratory flow was measured using a Wright peak flow meter (Airmed Ltd, Harlow England).

Volumes of expired air collected in Douglas bags during exercise were measured with a gas volumeter (Elster & Co AG 6503 Mainz Kastel, West Germany) and gas analyses were made as described by Haldane and modified by Enghoff (1946). A difference in the duplicate determination of less than 0.6 ml/l (fraction of oxygen) and less than 0.4 ml/l (fraction of carbon dioxide) was required during the course of the investigation.

Lactate concentration. Blood lactate was analysed, in series M1 and F as described by Barker and Summerson and modified by Ström (1949) and in series M2 and C according to Hohorst (1962). As calculated by analysis of variance the errors of sampling and analysis for the first method were 0.32 and 0.27 mmol/l, at a mean of 4.54 mmol/l and for the second method 0.50 and 0.19 mmol/l, respectively at a mean of 5.27 mmol/l. The consistency of the two methods was satisfactory the equation of the regression line being $y = 0.706X + 1.083$ $s_e = 0.873$ and $r = 0.85$ (or when the variables were expressed as logarithms $y = 0.803X + 0.103$ $s_e = 0.076$ and $r = 0.90$). The recovery of the second method, tested in whole blood, was 105.0 per cent at 4.5 mmol/l and 102.5 per cent at 8.5 mmol/l.

Heart volume. Heart volumes were measured by X-ray in the supine position as described by Bergstrom *et al.* (1969) with straight frontal and lateral projections.

Haemoglobin concentration. Haemoglobin was analyzed as cyanmethaemoglobin.

Statistical methods, definitions, symbols, and abbreviations

Student's t-test for paired observations was used when testing differences in the same subjects between different measurements. Student's two-sample t-test was used when values of different groups were tested. In the tables and figures the mean of the total number of individuals taking part in the measurements, on a particular occasion, are indicated irrespective of whether that particular individual took part on other occasions as well. This sometimes creates a discrepancy between numbers of observations in the groups, on the one hand, and the numbers of the differences included in the t-tests for paried observations, on the other. However it was considered advisable not to omit ose subjects who were not represented on all casions, since then, data would have been wasted nd the mean values would have been less representative.

The following symbols for probability (P) levels of significance were used.

$P > 0.05$ not significant NS

$0.05 > P > 0.01$ probably significant

$0.01 > P > 0.001$ significant

$P < 0.001$ highly significant

In the tables, if not otherwise stated, asterisks in front of a mean value refer to comparison with the reference value in column III (= the value of the 3rd measurement). Asterisks behind a mean value refer to comparison with that value of the column immediately to the right (for column IV/0 with that of column I). Asterisks between lines refer to comparisons of the values immediately above and below the asterisks, and asterisks below the bottom line to comparisons of the values of that line and values of the top line.

In the tables mean values are designated by $\bar{X}$, standard deviations by SD and numbers by N. However for denoting mean values and standard deviations for calculated differences (Δ), $\bar{d}$ and SD_d are used.

0 I II III and IV in heads of columns in tables and in figures designate different occasions of measurements (see p. 13).

Subjects

Series M = M1 + M2 (male patients) F (female patients), and C (control subjects).

Measurements

All measurements were made in the same way on all occasions, if not otherwise stated, and took place in the morning or early afternoon 1—2 hours after the subjects had ingested a light meal.

Chapter 4
CLINICAL EVALUATION

Subjects and procedure

All subjects (chapt. 2) were included, and the procedures detailed in chapt. 3 were followed.

Clinical observations

The degree of physical activity during the last 6 months immediately prior to the illness was estimated from the history using a four grade scale (1 = sedentary work, no planned exercise in spare time, 2 = ambulatory or physically moderately demanding work, or sedentary work with planned exercise in spare time, 3 = regular physically demanding training such as running, swimming, football etc, at least twice a week, 4 = competitive sports).

The subjects were also classified into one of 3 classes with regard to their smoking habits (1 = nonsmokers, 2 = 1—15 cigarettes, 3 = more than 15 cigarettes per day).

On each occasion of measurements the patients were carefully questioned about their average level of physical activity and smoking habits since the preceding occasion and these data were compared with those during the 6 months immediately preceding the illness.

On occasion I nearly all patients reported varying degrees of tiredness, tendency to sweating, and feeling of dizziness. Many of the patients suffering meningoencephalitis also complained of headache. Therefore, the subjects in series M2 and C were asked to estimate their subjective feeling of physical deterioration compared to the state before the illness, on each occasion of measurements, along a four-grade scale (0 = no, 1 = slight, 2 = moderate, and 3 = severe deterioration). All patients and control subjects were, on each occasion of measurements, asked whether they suffered any symptoms, and more specifically symptoms related to the heart or circulation.

A physical examination was performed on each occasion of measurements including auscultation of the heart.

Results

The degree of physical activity and smoking habits obtained from the case history are coded in Table V. There were no significant differences between the series. Since all patients had been confined to bed during the illness, and since discharge from hospital was followed by a period of convalescence (mean sick-leave being 16.5 days, range 0—46 days), the average level of physical activity between occasions I and II as compared to that during the 6 months prior to the illness was reduced in all the patients. On occasion III, six patients reported that they had still not reached their pre-illness levels of physical activity while one patient had surpassed it. Three patients stopped smoking in connection with their illnesses. On occasion IV most patients reported unchanged liv

Table V. Physical activity (PA) and smoking habits (SH) in patients prior to acute infectious disease and in control subjects prior to bed rest. (PA: 1 = sedentary life, 2 = ambulatory life, 3 = regular training, 4 = competitive sports. SH: 1 = nonsmokers, 2 = 1—15 cigarettes, 3 = > 15 cigarettes per day).

		PA		SH	
Series	N	$\bar{x}$	SD	$\bar{x}$	SD
M	47	1.8	0.8	1.6	0.9
		NS		NS	
C	22	1.9	0.9	1.3	0.5
		NS		NS	
F	33	1.6	0.6	1.4	0.5

ing habits but occasional changes were recorded in physical activity and smoking habits.

Tiredness, dizziness, and liability to sweating were reported in varying degrees by most of the patients on occasion I. Ten patients suffered headache. Most of the control subjects also reported some degree of tiredness. On succeeding occasions the presence or absence of these symptoms were more definitely stated by the patients. Thus, on occasion II, general tiredness was reported by 15 patients of 67 questioned (22.4 per cent) but only three suffered one of the other symptoms mentioned previously (4.5 per cent). All these symptoms had disappeared by occasions III or IV except in one man having suffered from mumps meningoencephalitis, who continued to complain of marked tiredness on occasion IV.

The subjective ratings of physical fitness on the different occasions are shown in Table VI. The ratings were significantly higher, i.e. corresponding to lower degrees of physical fitness, after illness/bed rest than on later occasions in both patients and control subjects, the patients giving higher ratings than the controls on occasions I and II. Correlations were performed of these ratings to the results of measurements of physical working capacity and orthostatic tolerance as described in chapt. 6 & 7.

In no case significant signs of heart disease were discovered at the physical examinations during the course of the investigation.

Table VI. Subjects ratings of own physical deterioration in a four-grade scale (0 = no, 1 = slight, 2 = moderate, and 3 = severe deterioration).

Occasions of measurements	M2 $\bar{x}$	SD	N	C $\bar{x}$	SD	N
I	2.3	0.6	11	1.0	0.8	22
II	0.8 NS	1.0	11	0.2 NS	0.4	22
III	0.4 NS	0.5	11	0.1 NS	0.4	22
IV/0	0.0 NS	0.0	11	0.1	0.4	–

Discussion

The degrees of physical activity and smoking habits prior to illness/bed rest were approximately similar in the male patients and in the control subjects, as expressed by the scales applied (Table V). However, there were some discrepancies. All but one in the control group were students. Some of them had work which was moderately demanding physically, but only part time and not continuous. Others worked only during the summer vacation. Among the male patients, on the other hand, 20 subjects (4_.6 per cent) had manual work which was ambulatory or moderately demanding physically, being employed as carpenters, factory-operatives, or drivers. Irregular exercise in spare time was more common in the control group, as was regular training. Two of the male patients, but none of the control subjects participated in competitive sports. Among the female patients the degree and proportion of occupational and recreational physical activity were similar to that of the control group. On average, the differences between patients and control subjects seemed small and may not be relevant. This problem will be discussed further in connection with the measured variables.

Since the patients had a normal convalescence with a mean sick leave of about 16 days, while the control subjects resumed normal activities immediately after discharge, differences between the groups in variables influenced by physical activity are to be expected on occasion II. On the other hand, the effects on mean values caused by alterations in physical activity and smoking habits, reported by a few subjects on occasions III and IV, should be minimal since the alterations were all small and occurred in both directions.

Symptoms such as general tiredness and increased liability to headache are known by the clinician to be common after acute infectious diseases. In retrospective clinical studies of the syndrome of neurocirculatory asthenia (NCA) a history of an acute infection is often encountered at the time of the start of NCA symptoms, and is therefore considered by many authors to be an important aetiological factor of this syndrome (Rotschild 1930, Jones et al. 1946, Ikonen 1951

Levander-Lindgren 1962, 1963). In later years, NCA has been shown to be associated sometimes with a hyperkinetic circulatory state (Holmgren *et al* 1957, Gorlin 1962, Frohlich *et al* 1969). Some of the patients of the present study reported symptoms found in the syndrome of NCA, namely tiredness, dizziness, cold hands or feet, and liability to sweating (Friedman 1945, Levander-Lindgren 1962), but other typical symptoms, such as precordial pain and palpitations were lacking. Bengtsson (1956) also found subjective asthenia symptoms to be rare after infections. As is described in chapt. 6 and 7, findings of decreased orthostatic tolerance and physical working capacity were made in the present cases, in similarity with cases of NCA (Cohen *et al* 1947, Holmgren *et al* 1957, Levander-Lindgren 1962), but these findings were not more pronounced in our cases reporting symptoms. Thus, it is not justified to designate the cases of the present study as suffering from milder forms of acute NCA, although Lyon (1952) described them after epidemic influenza.

In conclusion, from a practical and psychological point of view, it seems unnecessary or unjustifiable to term the present patients, showing only temporary symptoms, as suffering from this usually chronic disorder.

The results of the subjects' own ratings of their physical deterioration correspond to general clinical experience. Even only bed rest caused a significant subjective deterioration.

Chapter 5
RESTING MEASUREMENTS

Subjects and procedure

All subjects (chapt. 2) were included, and the procedures detailed in chapt. 3 were followed.

Measurements

Body height and weight were measured.

Heart volume was measured by X-ray

Heart rate, blood pressure, and respiratory rate were measured in the supine position prior to orthostatic tests and exercise tests. An ECG was recorded (results in chapt. 10)

Peak expiratory flow was measured with the ject sitting. The subject performed repeated (at 3) trials until consistent values were obtained *for at least 2 trials (difference not more than 20* l/min). The highest of these 2 values was used.

Haemoglobin concentration was measured using venous blood.

Results

Body height, body weight, and heart volume are shown in Table IX. Body weight was significantly lower after illness/bed rest (occasion I) than on later occasions in the male patients and in the control subjects, the mean difference between occasion I and III being 3.9 kg (5 1 per cent) in the male patients, 1 1 kg (1.5 per cent) in the control subjects. The means of the individual differences in body weight between occasions I and III (Δ body weight III—I) in these series, were significantly different ($p < 0 05$) The mean weight of the six control subjects who were strictly fasted decreased by 1 7 kg as compared to 1 1 kg in the others. The mean body weight of the female patients was 2.0 kg (3 4 per cent) lower on occasion I than on occasion III, a difference which was significant.

Heart volume did not change significantly between different occasions in any of the series. The male patients had larger heart volumes than the control subjects.

The resting heart rate and the systolic and diastolic blood pressures are included in Table X. There were no significant changes in heart rate on different occasions in the male patients or control subjects, but the female patients showed higher values after illness than on later occasions. Heart rate tended to be higher in the female patients than in the male patients, but the control subjects also showed somewhat higher values than the male patients, the difference becoming significant on occasion IV/0

No definite changes in resting systolic blood pressure were observed on the different occasions. However it was lower in the female patients than in the male patients or control subjects. The resting diastolic blood pressure was significantly lower in the control subjects than in the male patients, while the pressures of the latter were similar to those of the female patients.

No definite alterations in resting respiratory rate (Table XI) were observed in any of the series, except a *difference between occasions 0 and III in the control subjects, the rate being heigher on* occasion III.

The peak expiratory flow rate (Table XI) was significantly lower after illness than on later occasions, but this difference was not noted in the con trol subjects. The values for the women were lower than those for the men, the difference being high ly significant.

The haemoglobin concentration (Table XI) was significantly lower in the patients, males and fe males, after illness than on later occasions. Such a change was not recorded in the control subjects, the mean value being significantly higher than that of the male patients on occasion I.

The ECG findings are described in chapt. *10*

Discussion

When discussing shifts in body weight, changes in both fluid volume and solid matter ha e to be considered. Both patients and control subjects of the present study were influenced by the bed rest regimen and, at least some of them, by a shortage of calories. *In addition, the patients were influ* enced by the trauma of infection including the stress of a raised body temperature.

Evidence has gathered from a great number of bed rest experiments that plasma volume decreases during bed rest (Taylor *et al* 1945 Deitrick et al. 1948 Birkhead *et al* 1963 Miller *et al* 1964 B Vogt *et al*. 1966 Vogt & Johnson 1967 Vogt *et al*. 1967 Chobanian *et al*. 1974 Melada *et al*. 1975 Friman 1976 B) the decrease reaching its maximum within about two weeks (Vogt *et al* 1966 Vogt *et al* 1967). The results conflict over the involvement of the interstitial and intracellular spaces, in the fluid shifts induced by bed rest. Some authors have found a decrease of the total body water with bed rest (Vogt & Johnson 1967) or trends in this direction (Saltin *et al* 1968 A) while others have failed to reproduce these findings (Hyatt 1971). However negative sodium balance *occurs with bed rest* (Hyatt 1971 Hyatt *et al* 1975). In patients the picture is complicated by th trauma of infection and fever In early studies of infections accompanied by fever (Lustky & Friedstein 1920 Soule *et al* 1928 Altschule & Freedberg 1945) water retention was found to occur while in others no consistent change in blood volume was found (Ebert & Stead 1941 Rutstein *et al*. 1945). Later studies of pyrogen induced fever ha e shown no definite change in *blood volume (Gilbert 1960 Grimby 1962) There* ppear to be no recent studies of volumes of body fluid compartments during acute infectious disease Since the erythropoesis is inhibited by both bed rest (Lancaster 1969) and infection (Brown 1975) th haemotocrit cannot be used as an indicator of alteration in blood olume. However it is known from clinical routine that increased sweating is common with fever Thus, the turnover rate of sodium and w ter is increased and a decrease in body weight should f llow inadequat supplementation. On the other hand, the stress in duced by infection and fever (Cars & Friman 1976) might be associated with a sodium retention as occurs in surgical trauma (Le Queme & Lewis 1953). The final result of these possible mechanisms remains to be established.

The solid matter includes the lean body mass and the fat content. In bed rest experiments the variable beha iour of body weight has been ascribed to variations in the degree of immobilization and energy supplied (Taylor *et al* 1949). Only minor reductions (Cuthbertson 1929 Deitrick *et al*. 1948 Taylor *et al* 1949 Friman 1976, B) or no consistent changes (Saltin *et al* 1968 A) in basal metabolic rate have been found with bed rest, so that this factor can affect shifts in the total energy consumption only marginally In previous bed rest *studies body weight has changed only inconsistent* ly (Deitrick *et al* 1948 Birkhead *et al*. 1963 Saltin *et al*. 1968 A, Melada *et al*. 1975) or has decreased to a variable extent (Taylor *et al* 1949 Miller *et al* 1964 A Chobanian *et al* 1974).

Nitrogen balance has been the subject of special interest and study in relation to the influence of bed rest on physical fitness. In studies on four healthy subjects, Deitrick *et al* (1948) found an increase in nitrogen excretion beginning on the *5th day of bed rest. Cuthbertson (1929) had found* similar but less distinct results, but Birkhead *et al* (1963), using less strict immobilization, found no such increase. The activity during bed rest of the present study group was even less restricted than was the case in the four subjects f the study of Birkhead *et al* and the diet contained more protein. A negative nitrogen balance seems unlikely in the present control group at least in the 16 subjects who did not fast. This belief is supported *by recent findings of a retained positive* nitrogen balance despite complete bed rest for two weeks in adult volunteers, who were given 90—110 gram of protein daily (Mack & Montgomery 1973). The daily protein ration in the present control group was 115 grams.

Due to practical considerations, it was not possible to control the energy intake in the patients (e.g. sweets brought by relati es) and no definite statement based on personal observations can be made about possible *negati e energy balance*. However considering the additional energycon-

suming effects of the raised body temperature and trauma of infection (Hoepng 1972 Felig 1975) and the fact that most meals served were incompletely consumed when the patients had fever it seems highly probable that most patients expended more energy than they ingested. It is known from starvation experiments that the body adapts to decreased food rations by decreasing its total combustion (Keys *et al* 1950). However these adaptive mechanisms are not brought into action until several days after the onset of food deprivation (Felig 1975) and as mentioned previously the trauma of infection should work in the opposite direction by increasing the demands of energy

The significantly greater loss of weight in the male patients than in the control subjects, a trend which remained valid even with fasting subjects, should be caused by mechanisms specific for febrile illnesses such as relative shortage of energy salt and fluid. When expressed in percentage a similar difference between the female and the control subjects seems probable although not statistically proven. However the mean durations of illness, fever and bed rest were somewhat shorter in the female patients than in the male patients, that of bed rest significantly so (Table III).

In large series a high correlation has been found between heart volume and other measures of circulatory function, such as working capacity and total haemoglobin (Kjellberg et al. 1949 A and B) so that the present finding of larger heart volumes in the male patients than in the control subjects may indicate that the patients had greater circulatory dimensions. *Another possible explanation is* sequelae of inapparent myocarditis in the patients, an explanation which seems improbable due to lack of other signs of such a state (see capt. 4 and 6) The former explanation is supported by the slightly although not significantly higher body weights of the patients (Kjellberg *et al* 1949 A). These points are discussed further in chapt. 6 where training aspects are considered. The variation in the difference of mean heart volume between male patients and control subjects at different measurements has not been definitely established, since this variation falls within the error of the method. The error was assessed using the determinations on occasions 0 and III in 21 healthy control subjects, assuming that, on average their degree of training was unchanged, an assumption based on the history and unchanged W_{max} perf (Table XIV) However since a systematic difference could not be excluded the formula $\sqrt{\frac{\Sigma(D-\bar{D})^2}{2\ (n-1)}}$ was used, giving an error of the single determination of 69 4 ml or 9 7 per cent of a mean heart volume of 718.5 ml.

In Bengtsson's study heart volume was 150 ml smaller after illness than one month later a difference which was almost significant (Bengtsson 1956). However working capacity expressed as W_{170}, differed by 34 6 watts between the group investigated after illness and that investigated 1 month after illness as compared to 12.3 watts in series M2 of the present study Results of the effect of bed rest on heart volume are conflicting. Thus, some investigators have found a decrease or a tendency in that direction (Taylor *et al.* 1949 Saltin *et al.* 1968 A, Krasnykh 1970 1974) while others have recorded *no consistent change* (Deitrick *et al* 1948 Sokoll *et al* 1973).

In the patients, but not in the control subjects, higher heart rates were recorded on occasion I than on later occasions, a difference which was significant in the females. Alterations in the myocardium of a similar type to those shown in skeletal muscle in viral and mycoplasma infections (Åström *et al* 1975) seem plausible but have as yet not been demonstrated. Normal electrocardiograms do not invalidate this suggestion since ECG findings cannot at present be correlated with the *ultrastructural picture of the myocardium in these* illnesses. Thus, myocardial involvement might have caused the higher resting heart rates in the patients after illness, but increased sympathetic tonus would give the same result. In most previous studies, increased resting heart rates have been demonstrated after bed rest (Deitrick *et al* 1948 Taylor *et al* 1949 Birkhead *et al.* 1963 Saltin *et al* 1968 A). However in two recent studies (Chobanian *et al* 1974 Melada *et al.* 1975) as in the present one, no alteration in resting heart rate was recorded. The bed rest periods of the former studies ranged from 3 to 7 weeks, those of the

latter from 5 days to 3 weeks, this difference being a possible explanation of the differences in findings.

Higher resting heart rate values in women than in men have been found in earlier investigations (Altman & Dittmer 1971 Friman & Waern 1974). Since the stroke volume is correlated to the heart volume (Holmgren *et al* 1960) the lower heart rates in the male patients than in the control subjects, significant on occasion IV/0 might result from higher resting stroke volumes in the patients. Alternatively there could have been greater apprehension in the control subjects who were to perform a maximal work test shortly after the heart rate recordings, than in the patients who were subjected to submaximal tests (chapt. 6).

The resting blood pressures (BP) systolic and diastolic, were not significantly influenced by illness/bed rest in either of the series. The significant difference in systolic blood pressure noted on occasions I and III in the male patients was not confirmed on comparing BP on occasions I and IV In most previous studies resting supine blood pressure has been unchanged with bed rest (Deitrick *et al.* 1948 Taylor *et al.* 1949 Saltin *et al.* 1968 A Chobanian *et al* 1974 Meleda *et al.* 1975). The consistently higher systolic blood pressure and the tendency towards lower diastolic blood pressure in the male patients and control subjects, than in the female patients accord with findings in these age groups in large population studies of blood pressure (Hamilton *et al* 1954). However the difference in diastolic blood pressure between male patients and control subjects remains unexplained.

It is known from previous studies of respiratory infections with (Berven 1962) and without (Kennedy *et al* 1965 Johansson *et al.* 1969) apparent lower respiratory tract involvement that the breathing capacity and oxygenation of the blood may be impaired. Further compliance changes compatible with small airway involvement have been demonstrated with upper respiratory tract infection (Picken *et al.* 1972). However signs of bronchial obstruction were not recognized in these studies. Thus, the present findings of significantly lower peak expiratory flow (PEF) values on *occasion I than on later occasions in the patients* but not in the control subjects may be ascribed to extrapulmonary factors. Since the maximal isometric muscle strength of the extremities has been shown to be reduced after acute febrile infections (Friman 1976 A), decreased strength of the respiratory muscles seems the most probable cause of the differences in PEF The importance of the muscle mass for the outcome of PEF has been stated before (Dobeln 1968) All values recorded lay within the normal ranges indicated by Adolfsson *et al* (1968) and Källqvist *et al* (1970).

The rise in haemoglobin concentration in the patients on occasions I through IV in the male patients finally to reach the level of the control subjects, may be considered as part of the clinical picture in the present illnesses (Brown 1975).

suming effects of the raised body temperature and trauma of infection (Hoeprig 1972, Felig 1975) and the fact that most meals served were incompletely consumed when the patients had fever it seems highly probable that most patients expended more energy than they ingested. It is known from starvation experiments that the body adapts to decreased food rations by decreasing its total combustion (Keys *et al* 1950). However these adaptive mechanisms are not brought into action until several days after the onset of food deprivation (Felig 1975) and as mentioned previously the trauma of infection should work in the opposite direction by increasing the demands of energy

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cise tests were performed on two consecutive days in order to determine the extent of day-to-day variation in heart rate response.

The results of W_{150}, irrespective of degree of extrapolation necessary were compiled according to diagnosis groups (Table XII).

For each series of subjects and for diagnosis groups the amount of work performed, $W_{max\ perf}$ (Strandell 1964) on each occasion was calculated for those cases who indicated code No. 2 or 3 when rating the degree of exhaustion at the end of the exercise test

Results

The complete results of the xercise tests are included in Tables VII and XIII—XVII and Fig. 1

The subjects were classed into one of five classes on each occasion of measurements depending on which symptom they indicated as dominating *during the last minutes of work. The percentage* of subjects belonging to each class on each occasion are shown in Table XIII. These figures tend to underestimate the variation since the existence of simultaneous changes of classes in opposite directions from one occasion to another does not necessarily influence the percentage figures. However a complete description of these data would not be surveyable or too voluminous. A few trends can be gathered from table XIII.

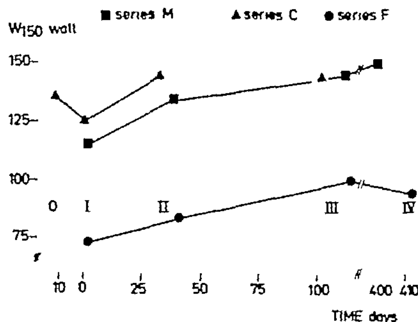
Thus, specific symptoms, usually headache, were, as expected more common after illness than on later occasions. Shortness of breath tended to bo *more common on occasion I Tiredness of legs*, on the other hand, was less common directly after illness than on later occasions. General tiredness tended to increase m percentage from occasions I through IV In the control subjects shortness of breath was also more frequent on occasion I, while general tiredness, as in the patients, increased in percentage on later occasions.

In a similar manner the degree of exhaustion as rated by the subjects is presented in Table XIII The highest ratings of exhaustion were more common on occasion I than on later occasions in the patient series. On the other hand, there was no definite trend in the frequencies of low ratings of exhaustion on different occasions (except on *occasion IV) and thus the sum of ratings of codes* and 3 were roughly constant at least on occasions I through III (range 71.5 — 83 8 per cent) in the patient series. This fact lends support to the significance of differences in $W_{max\ perf}$ (see below). The control subjects always rated the highest degree of exhaustion.

The pulse related physical working capacity (W_{HR}) is shown in Tables VII and XIV and in Fig. 1 In Table VII the mean of occasion III (Table XIV) was set to 100 per cent for each series of

Table VII Physical working capacity (W_{HR} and $W_{max\ perf}$) in patients and control subjects expressed as percentages (%) of values on occasion III (= reference levels)

	I		II		III		IV/0	
	%	N	%	N	%	N	%	N
W_{150}								
Series								
M	76.8	43	91.3	37	100.0	31	107 1	27
C	83.6	22	99 1	22	100.0	21	92.8	22
F	61.5	31	81.8	29	100 0	28	93 8	30
W_{130}								
Series								
M	79.3	44	92.6	37	100.0	31	103 4	27
C	86.9	22	100.2	22	100.0	21	94 4	22
F	72.7	32	83 4	29	100 0	28	94 1	30
W_{170}								
Series								
M2	85.3	12	92.3	12	100.0	12	100.5	12
C	90.5	22	100.8	22	100.0	21	96.5	22
$W_{max\ perf}$								
Series								
M	77.2	36	93.2	31	100.0	25	108.4	24
C	95.6	22	100.4	22	100.0	21	99.2	22
F	73 6	28	89 7	24	100.0	20	104.3	26



1 Physical working capacity (W_{150}) in patients, males (series M) and females (series F), and in con- subjects (series C).

subjects, because the results on this occasion about 3½ months after illness/bed rest, are considered to be reasonably representative of the habitual level of the individual. In Table XV the means of the individual differences in working capacity between different occasions (ΔW_{150}, ΔW_{130}, and ΔW_{170}) are included.

Thus, according to Table XIV in the male patients, the physical working capacity immediately after illness was reduced by 25.5 — 30.0 watts, depending on which reference heart rate was chosen. The deterioration in women was of the same order of magnitude in absolute terms, with reductions of 27.4 — 28.3 watts, the respective values of the control subjects being 17.3 — 18.8 watts. However the differences between reductions (ΔW_{150}, ΔW_{130}, and ΔW_{170}) in patients and control subjects were not significant (Table XV) nor were there any significant differences in absolute levels for male patients and control subjects on any occasion of measurements (Table XIV). Due to their lower habitual level, the deterioration in the female patients was greater than that of the male patients when expressed in relative terms. Further there was a trend for the rate of recovery in both absolute and relative terms, to be slower in the females. After one month they had regained less than half of their total deterioration expressed as W_{150}, while the male patients had about surpassed this limit by that time. The control subjects had then reached their habitual level (Tables VII and XIV).

The results of the calculations of W_{150}, W_{130}, and W_{170} after exclusion of those occasions when extrapolation of more than 10 beats had been made did not differ significantly from those obtained in the total series.

The extent of variation in HR response to exercise in tests performed on two consecutive days, mostly directly after illness, expressed as the error

of the single determination of $W_{1.a}$, was 5 19 watts of a mean of 102.01 watts.

On an average the differences in pulse-related working capacities on different occasions were of the same absolute order of magnitude within each series of subjects irrespective of which pulse rate was chosen as a reference. This indicates roughly parallel pulse/load regression lines on the different occasions of measurements.

The results of W_{130} when arranged according to diagnosis groups are shown in Table XVI. The only significant differences noted were those on occasions I and II between men suffering from pneumonia when compared to men with other diagnoses, the pneumonia cases having a lower W_{130} mean. A trend in the same direction could be recorded in the women. When testing ΔW_{130} of diagnosis groups a significant difference was noted in $\Delta W_{130\ III—I}$ between men suffering from meningoencephalitis and men suffering from other viral or mycoplasma infections, the former having lost less in working capacity ($p < 0.05$). The women showed no such difference. A significant difference was also noted in $\Delta W_{130\ II—I}$ for female pneumonia patients as compared to those with other diagnoses ($p < 0.05$)

On occasion I, the W_{130} mean of the men suffering from pneumonia was significantly lower than that of the control subjects ($p < 0.01$) Similarly $\Delta W_{130\ III—I}$ was greater in these patients than in the control subjects ($p < 0.05$).

The results of $W_{max\ perf}$ and $\Delta W_{max\ perf}$ in different series of subjects are included in Tables VII, XIV and XV

The decrease in $W_{max\ perf}$ after illness was of about the same magnitude in all series of patients as that of W_{130} when expressed as percentages of reference levels of occasion III (Table VII). On occasion II only the fraction of $W_{max\ perf}$ of the female patients differed to some extent from that of W_{130} on the same occasion being higher in $W_{max\ perf}$ and the absol te values of $W_{max\ perf}$ of occasion II (Table XIV) differed significantly from those of occasion III only in the female patients. The control subjects, on the other hand, performed an amount of work on occasion I corresponding to 95 6 per cent of that of occasion III, the corresponding figure of W_{130} being 86.9 per cent and of W_{170} 90.5 per cent. Since the control subjects performed maximal work on all occasions, they achieved considerably higher absolute levels than the patients $\Delta W_{max\ perf}$ (Table XV) reached significantly lower values in the control subjects than in the patients among whom no difference between sexes could be demonstrated.

When testing $W_{max\ perf}$ in diagnosis groups (Table XVI) no significant differences could be found. A probable difference was noted between male patients suffering from pneumonia and those with other diagnoses but the numbers of male pneumonia patients was low A similar difference ($p < 0.05$) was noted between female patients with bacterial as compared to other infections when testing $\Delta W_{max\ perf\ II—I}$. However the numbers were again low

Several correlations were performed (Table XVII). The deterioration in the different pulse related physical working capacities calculated (W_{HR}) were significantly correlated to the duration of bed rest but less so to the duration of illness and fever Correlations to the decrease in $W_{max\ perf}$ were lower and non-significant. There was a significant correlation of the decrease in W_{HR} to reference levels of W_{HR} only in the female patients. The subjects own ratings of their physical deterioration were not correlated significantly with duration of illness, of fever or of bed rest, or with decreases in W_{HR} The level of physical activity was correlated significantly to reference levels of W_{HR} only in the male patients, the correlation coefficients being for W_{130} 0.58 ($p < 0.001$) and for W_{170} 0 68 ($p < 0.05$).

Using multiple correlation analysis in the male patients and control subjects with duration of bed rest, duration of fever and level of physical activity as independent variables the only significant factor was found to be duration of bed rest.

In the female patients, the systolic blood pressure during exercise tended to be higher on occasion I than on succeeding occasions, a difference being significant only on the lowest load ($p < 0.05 — 0.01$). No consistent changes were observed in the male patients and control subjects.

Discussion

Headache was a common complaint after illness in patients suffering from meningoencephalitis, and was indicated as the dominating symptom during the exercise test by many patients, especially females (Table XIII). The tendency for shortness of breath to be more common on occasion I than on later occasions is probably associated with the findings of higher respiratory rate and ventilation after illness (Table XX). This matter will be further commented on in chapt. 8.

The trend for a successive shift from local to general symptoms from occasion I through IV might be explained by the disappearence of symptoms related more specifically to the illness and their replacement by symptoms of general fatigue and exhaustion which limit heavy work under normal conditions. Thus, in contrast to the findings with , -- after thermal dehydration (Saltin 1964), .. of legs was not the dominating limiting factor after illness/bed rest. The focal alterations in the ultrastructure and reduced activities of oxidative and glycolytic enzymes found in biopsies from the quadriceps muscle of series M2 on occasion I (Åström *et al.* 1975, 1976 A) *therefore* appear not to be associated with increased symptoms from the legs during exercise under the present conditions of testing. Not unexpectedly the degree of exhaustion was rated higher after illness than on later occasions, since after illness it was sometimes necessary to encourage the patients more to make them *reach heart rates high enough* to enable calculations of W_{HR}. Despite this, extrapolations of more than 10 beats had to be made on 10 occasions.

It cannot be excluded that the room temperature, being higher during the summer months, however not exceeding 25 C, might have influenced the results of the pulse related physical working capacity (W_{HR}) to some extent (Saltin et al 1968 B). This influence might, however, have been insignificant *when total series are considered* since firstly no measurements were performed for 2 months in the middle of the summer and secondly patients were included consecutively and at a fairly constant rate during the rest of the year. Similarly the 6.7 and 5.1 per cent lower haemoglobin concentrations observed in male and female patients after illness than on occasion III probably had only minor effects on heart rate response to exercise (Ekblom *et al.* 1972).

In the patients, the decrease of W_{HR} was of the same magnitude, in absolute terms, in males and females, despite the appreciable difference of the size of their oxygen transporting organs. The decrease was significantly correlated to the duration of illness and, especially to the duration of bed rest in both sexes (Table XVII) and there were no differences in these variables between the sexes to account for the relatively more pronounced deterioration in the women. On the contrary the duration of bed rest was .. days shorter in the female patients (Table III). A relatively more pronounced deterioration of W_{HR} in women than in men was also found by Bengtsson (1956) in his study of patients hospitalized with various acute infectious diseases without cardiac complications. Thus, whether or not the percentual difference in deterioration of W_{HR} is due to difference in sex cannot be established. It would appear more fruitful to discuss this difference in relative deterioration in terms of degree of physical training.

Adolfsson (1969) subjecting female patients to physical training prior to cholecystectomy found the operation and bed rest to cause greater deterioration, even in relative terms, in those who had trained than in control patients. Bassey & Fentem (1974) found the same pattern of response to meniscectomy and bed rest for two weeks in nine healthy males of 20 to 49 years of age, those with the best *initial physical condition* deteriorating more than those with a lower physical capacity. Further these authors, using data from the bed rest study of Saltin *et al.* (1968 A), found a similar pattern in the five subjects of that study. In the present study such a relationship is not evident when the total series (M + C + F) are considered, the coefficient of correlation (r) between initial fitness, expressed as W_{150}, and deterioration ($W_{150\ III-I}$) being 0.04. In the female patients, however, r $W_{150\ III}/W_{150\ III-I}$ was positive and significant, as was r $W_{HR\ III}/W_{HR\ III-I}$ and r $W_{max\ perf\ III}/W_{max\ perf\ III-I}$, whilst in the male patients these coefficients were lower al-

though still positive. The control subjects showed still lower coefficients (Table XVII). The findings of Adolfsson (1969) and Bassey & Fentem (1974), referred to above, probably expresses a funda mental relationship the reverse of which is valid with physical training (Saltin *et al.* 1968 A Kil bom 1971 Nordesjo 1974). In other words, training of the same amount and relative intensity causes greater absolute changes in physical fitness in individuals of lower than of higher degrees of pre-existing physical fitness (degree of physical training). This implies that the female patients of the present study had a higher degree of fitness before illness than the male patients. According to levels of physical activity and smoking habits noted in the case histories (Table V) there are no indications of such a difference. In a training study by Nordesjö (1974) a significant positive corre lation was found between capacity for short work and the level of recreational but not occupational physical activity These forms of activity were not discriminated in the present study but, neverthe less, the overall" activity correlated positi ely and significantly with the reference level of physical working capacity in the male patients but not in the female patients. This difference might be attributable to a lower variance of the component of recreational activity in the overall" figure for the females but, from the information a ailable, it is not possible to infer that the women would have a higher degree of physical fitness than the men. In the control subjects, whose physical activity was mainly recreational, a weak correlation to performance was found, which might be compatible with a low ariance m the recreational component

Although, the mean deterioration in W_{HR} of the control subjects of the present study was only 65 per cent of that of the male patients the scatter was too great to be significant (Tables VII XIV and XV). With some reason it could be argued that the control subjects were probably on a higher habitual training level than the male patients, since their W_{HR} were the same, but their heart olumes lower and their body weights slightly lower This suggests a real difference although significant only in the pneumonia patients, in de gree of deterioration brought about by illness/bed rest as compared to bed rest alone. The existence of such a difference is supported by observations in athletes, whose heart rate response to submaximal exercise is often significantly increased when they suffer acute upper respiratory infections, even before definite clinical symptoms are apparent (B Ekblom, personal communication). Thus, although not proven, there does seem to be additional de terioration brought about by the illness as such, but the stronger correlation of the deterioration to the duration of bed rest than to the durations of illness and fever speaks in favour of bed rest being the most important factor

The greater deterioration in patients suffering from pneumonia (Table XVI) may be ascribed to the more intense disease process in this illness compared to most other illnesses studied, rather than to the somewhat longer bed rest time (Table XII). Similar differences in W_{HR} between pneu monia patients and patients suffering from other infectious diseases was found by Berven (196). On the other hand, the explanation of the lesser degree of deterioration encountered in the male patients suffering from meningoencephalitis than in those suffering from other viroses seems less clear

As has been pointed out by Rowell *et al* (1964) non-specific stresses may influence the heart rate response to upright exercise to give falsely low values of working capacity when expressed as pulse related work or in terms of maximal aerobic power calculated from W_{HR} by the nomogram of Åstrand & Rhyming (1954) Thus, Chase *et al.* (1966) found no decrease in observed maximal oxygen uptake after bed rest for 15 days in contrast to a significant deterioration in W_{HR}. Similar results have been found during pyrogen-induced fever (Grimby 1962) and after thermal de hydration (Saltin 1964). After experimental malaria, on the other hand, the maximal oxygen uptake was lower than before inoculation of the plasmodia (Henschel *et al* 1950). However this might ha e been accounted for by a concomitant decrease in the haemoglobin concentration of 21.9 per cent. The plasma volume remained constant. In the present study haemoglobin concentration was only 5 0 — 6.7 per cent lower after illness than on occasion III. In the malaria study a sig

nificantly increased heart rate response to standardized treadmill exercise was not found for more than 24 days after cessation of fever The illness had been terminated after 5—8 paroxysms, and the subjects were confined to bed only when febrile spending the intervening time working, with daily walks uphill on the treadmill for one hour a regimen which probably accelerated the recovery The present author has found no other study in the literature of the influence of acute infectious disease on the maximal aerobic power

Bengtsson (1956), using submaximal upright bicycle exercise tests, found lower W_{170}-values in his patients 1 month after discharge from hospital than in a control group. The time required for restitution of the heart rate response to exercise of more than one month accords with the findings in the present study despite the differences in mean durations of illness and bed rest, the former . 2.5 weeks, the latter 2.3 weeks in Bengts- study as compared to 9 6 and 7 6 days, res- ly in the present investigation. However differences in diagnoses and hospital routine render comparisons difficult.

It is known from studies on normal subjects that W_{HR} is not influenced much by the body position a lower cardiac output at work in the sitting position usually being compensated for by an increased arteriovenous oxygen difference (Bevegård *et al* 1960). However after bed rest, Birkhead *et al* (1963) in one of his cases, found a higher heart rate response to submaximal work in the upright than supine position, due to an appreciable difference in stroke volume. Likewise Berven (1962) noted a minor difference in the same direction of heart rate response to a given load, supine and upright, in cases convalescing after various acute infectious diseases, mostly pneumonia. Some authors attribute all the deterioration in W_{HR} on upright exercise after bed rest to impaired venous return (cf discussion in Saltin *et al* 1968 A), but the studies by Saltin et al. (1968 A), using both supine and upright exercise rule out venous pooling as the sole mechanism.

Some of the patients of the present study (9 1 per cent of the males and 14 7 per cent of the females) indicated no symptom during work on occasion I (Table XIII), the work tests in most cases being interrupted by the author due to high heart rates. Due to the apparent lack of association between heart rate response and degree of exhaustion in these cases, it appeared worthwhile to express working capacity in terms of W_{max} perf in addition (Strandell 1964) However to increase the accuracy of this designation, those subjects were excluded who did not reach a certain degree of exhaustion (see chapt. 3). Notwithstanding this reduction of the series and as far as the patients are concerned, W_{max} perf can still be considered a clinically determined measure which is, however not to be compared with the work performed by the control subjects, who had a higher level of motivation. On average W_{max} perf was found to follow W_{130} when expressed as a percentage of the values of occasion III in the patients, while in the control subjects higher intensity was performed on occasion I than the calculated W_{130} or W_{170}.

The results of the calculations of the heart rate response to exercise on the 9 occasions when an exercise test was performed on two consecutive days showed no consistent change to suggest better working capacities on the second day Therefore the possibility of an increased effect of habituation after illness/bed rest can be rejected (for review see Nordesjö 1974).

No change in physical working capacity caused by administration of antibiotics should be expected (Furberg & Ringqvist 1963).

The lack of consistent change in working systolic blood pressure on the same absolute loads are not in accordance with the findings of earlier investigators. Saltin *et al* (1968 A) found lower systolic blood pressure on the same absolute submaximal loads of treadmill work after bed rest than during a control period, and Bassey *et al* (1973) recorded lower systolic blood pressure on the same relative work load in the sitting position after bed rest in patients confined to bed for meniscectomy than before the operation. The trend in the females of the present study to have higher blood pressure after illness, although having been confined to bed, lends additional support to a difference, which might be ascribed to sympathicotonia.

Chapter 7
REACTION TO STANDING (ORTHOSTASIS)

Subjects and procedure

All subjects (chapt. 2) were included and the procedures detailed in chapt. 3 were followed.

An orthostatic test was conducted prior to the exercise test with the subject standing. The subject first rested for at least 15 minutes in the supine position while the ECG was recorded and heart rate and blood pressure were measured as described in chapt. 3.

Measurements

During standing, measurements were made every second minute.

Besides the recordings of heart rate, systolic and diastolic blood pressures were measured every second minute during standing, the highest attained heart rate on standing (HR_{max}), the difference between HR_{max} and the resting heart rate (peak heart rate increase from supine to standing) and the mean heart rate during standing were calculated. Additional calculations included the lowest systolic blood pressure, the mean systolic blood pressure, the highest diastolic blood pressure, the mean diastolic blood pressure, and the lowest pulse pressure on standing. Finally HR_{max} was tested with the patients grouped in diagnosis groups (Table XII) to reveal possible differences attributable to diagnosis or aetiology.

Results

The principal results of the orthostatic tests are included in Tables XVIII—XIX and in Fig. 2. Thus, in th patients HR_{max} and mean heart rate during standing were bout 20 beats per minute higher after illness (occasion I) than 3 / months later (occasion III), and there were no significant differences between th sexes (Table XVIII). The same principal pattern was seen when calculating the individual peak heart rate increase from supine to standing, these alues being significantly higher on occasion I than on later occasions in both male and female patients ($p < 0.001$) but on the same level in the control subjects. After 1 month (occasion II) there was still a higher heart rate response, although this was significant only in the male patients. In the control subjects, on the other hand, the response was of the same magnitude on all occasions, being lower than that of the patients on occasion I, higher on occasion III (Table XVIII). Further evidence of a difference between the patients and the control subjects, even on occasion II, was provided by performing group-t tests of the heart rate differences between different occasions of measurements (ΔHR_{max} and Δ mean HR) (Table XIX). Δ peak heart rate increase from supine to standing showed the same pattern of response as ΔHR_{max} and Δ mean HR, the differences between patients and control subjects being significant ($p < 0.01$).

The systolic blood pressure (lowest or mean) during standing was significantly lower in the female patients than in the male groups on all occasions, except on occasion I (only the latter variable included in Table XVIII, since trends and significance levels were principally the same in both ariables). This latter observation was apparently due to the fact that the systolic blood pressure of the male patients during standing was 9—10 mm Hg lower on occasion I than on occasion II, while this difference only amounted to 3—4 mm Hg in the women. The control subjects showed no such difference (Table XVIII and Fig. 2). When testing these differences in mean systolic blood pressure (Δ mean systolic BP) by means of group-t-tests the differences between male patients and control subjects was significant (T ble XIX). Further the equivalent differences were tested

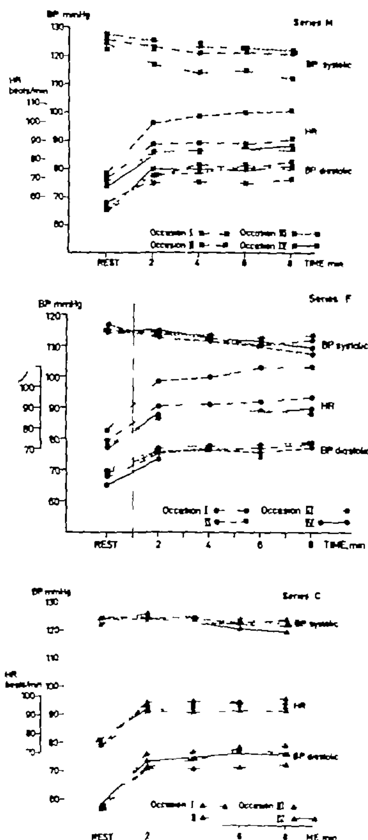


Fig. 2. Heart rate and systolic and diastolic blood pressure at rest and during 8 minutes of standing (orthostatis) in patients, males (series M) and females (series F) and in control subjects (series C).

using the results of the every 2nd minute measurements (Fig. 7). Then significant differences between sexes in the systolic blood pressure difference were established at 2 minutes between occasions I and III ($p < 0.05$) and between occasions I and IV ($p < 0.05$) at 4 minutes between occasions I and IV ($p < 0.05$), at 6 minutes between occasions I and II ($p < 0.05$) and between occasions I and IV ($p < 0.001$).

The diastolic blood pressure (highest or mean) during standing in the male patients and in the control subjects was significantly lower after illness/bed rest than one month later but the group means were not significantly different on comparable occasions. The female patients did not alter their diastolic blood pressure (highest or mean) between different occasions of measurements (only mean diastolic blood pressures included in Table XVIII by the same reason as for systolic blood pressure). This difference between sexes is further illustrated by a significant result when testing the differences in mean diastolic blood pressure (Δ mean diastolic BP) between occasions I and II (Table XIX) and when testing the equivalent difference recorded in the 8th minute of standing ($p < 0.05$).

The lowest pulse pressure during standing was significantly lower after illness than 3 / months afterwards in the male patients but not in the female patients, in whom an insignificant reduction was recorded. The control subjects, on the other hand, increased their pulse pressures after bedrest. Noteworthy is also the finding of significantly lower pulse pressures in the women than in the men, both when the women were compared with the patients and with the control subjects, differences thus mainly accounted for by differences in the systolic blood pressure level.

HR_{max} and ΔHR_{max} for different diagnosis groups (Table XII) were calculated. Observations from men and women were pooled, since they showed no significant differences in the present variables on any occasion. Significantly higher HR_{max} values were seen on occasion I in the patients suffering from pneumonia than in the other patients ($p < 0.05$) a difference which became highly significant when the variable ΔHR_{max} was tested ($p < 0.001$). All other comparisons (in analogy with variables in Table XVI) were insignificant.

The degree of orthostatic dysfunction in terms of heart rate reaction (HR_{max} I—III) was positively and significantly correlated to the duration of bed rest, especially in the male patients, and to the duration of fever (Table XVII). On the other hand, the subjects' own ratings of their physical deterioration yielded low coefficients in all series.

On occasion I two male and one female patients suffered a vasovagal reaction. No such reactions were encountered on later occasions.

Discussion

The type of orthostatic reaction which is to be expected in healthy young adults is the sympathicotonic type occasionally merging into a vasovagal reaction (Thulesius 1970). In Thulesius' series the latter reaction only occurred in young men. Since the sympathicotonic reaction of tachy*cardia is triggered in order to maintain mean ar*terial blood pressure (BP) in the face of a fall in cardiac output (pulse pressure), due mainly to deficient venous return (Weiss *et al.* 1937, Browse 1965, Thulesius 1970), measurements of BP and heart rate (HR) are relevant. There are different procedures to conduct an orthostatic test and to process its results (Graybiel & McFarland 1941, Vogt 1966, Shvartz 1968, Hyatt *et al.* 1975). No significant difference between the values of the peak HR increase from supine to standing was obtained when using passive standing and when using the tilt board in the control group of the present study (Friman 1976 B), thus confirming earlier results (Hyatt *et al.* 1975). The three most reliable measures of each of HR, systolic BP and diastolic BP were used (Shvartz 1968) to diminish the influence of disturbing factors (Stevens 1966, Kilbom 1971). The tests were conducted for 8 minutes, according to our laboratory routine, since representative changes of cardiac output occur during that time (Tuckman & Shillingford 1966, Thulesius 1970, Kilbom 1971).

The findings of more pronounced responses in HR and BP in the patients after illness than in the

control subjects after bed rest accord with previous clinical observations of symptoms possibly referable to orthostatic dysfunction after acute infections (Stuart Harris 1965 Emminger & Kaiser 1970) and with reports of measurements of HR and BP after such diseases (Henschel *et al* 1950 Bengtsson 1956, Berven 196_). However prospective controlled studies of orthostatic tolerance, as *in the present study have not been published to* date. There was a difference between the male and female patients in their systolic BP responses, the women keeping their pressure at the same level (except on the 8th minute of standing) on all occasions, while the men s systolic BP after illness was at a lower level during standing. In the control subjects, the reduction of diastolic BP after bed rest was more pronounced, but significant alterations of HR and systolic BP reactions were lacking. Thus, the present bed rest regimen did ot influence orthostatic tolerance to a discernible ree. This is not in accordance with earlier in tigations in which a substantial orthostatic dysfunction has usually been observed after bed rest (Deitrick *et al* 1948 Taylor *et al* 1949 Gra e line & Barnard 1961 Birkhead *et al* 1963 Miller *t al* 1964 A and B Vogt *et al. 1966* Vogt *et al* 1967 Saltin *et al.* 1968 A, Kotovskaya *et al* 1970 Pestov *et al* 1970 Chobanian *et al* 1974 Melada *et al* 1975 Hyatt *et al* 1975). However these investigations were not concerned with clinical bed rest but instead with strict immobilization *of longer duration than one week. Deitrick et al* (1948), for instance, found the deterioration to commence within the first week but the reactions became more pronounced during the later stages of their bed rest regimen.

In conclusion the present results may be interpreted as indicating that infectious disease *per se may bring about a substantial orthostatic dysfunction.*

Previous investigators (Graybiel & McFarland 1941 Deitrick *et al* 1948) found the pulse pressure to be the variable best correlated with the subject s own reaction symptoms occuring when the pulse pressure fell to 10—1_ mm Hg. This was also observed in all those patients, who suffered a vasovagal reaction. However there was a sex difference in the present study the women showing a consistency of orthostatic diastolic BP as opposed to the men. Another factor of importance may be the effect of blood volume changes on orthostatic function. On this problem, the literature is conflicting (Miller *et al* 1964 B Stevens *et al* 1966 Vogt *et al* 1966 Vogt *et al* 1967 Vogt & Johnson 1967 Hyatt 1971).

HR_{max} during standing showed the same pattern of response as that of W_{130} when calculations were made for different diagnosis groups. Patients with meningoencephalitis did not show responses different from those of the others, although there are indications in the literature of the possible existence of such a difference (Thulesius 1973).

Correlations are shown in Table XVII The lack of a correlation between the subjects own ratings of their physical deterioration and degree of orthostatic dysfunction (as of physical working capacity *chapt. 6) should be interpreted as an illustration* of the importance of psychological factors and of the psychic constitution in the evaluation of personal fitness.

Chapter 8
VENTILATION AND GAS EXCHANGE

Subjects and procedure

Only series M2 and C (chapt. 2) were included in the present study The procedures detailed in chapt. 3 were followed.

Measurements

Expired air was collected in a Douglas bag during the last 2 minutes of each load of the exercise test for determination of ventilation oxygen uptake, and carbon dioxide production. On those occa sions when a load could not be maintained for 6 minutes, in order to be accepted, gas collections had to be performed for at least 1 minute, not earlier than during the 2nd minute of work on that load.

Results

The main results of the studies of entilation and gas exchange on the three lowest work loads are shown in Table XX together with the 6 minute heart rate and oxygen pulse Data from higher loads are not included since the numbers of observations on those loads are too few to permit accurate comparisons.

In the patients, respiratory rate and ventilation volume tended to be higher on occasion I than on succeeding occasions, although this was significant only in some instances. In the control subjects the respiratory rate and ventilation did not change between different occasions (except be tween occasions 0 and III on the 147 watt load, ventilation being higher on occasion III) and were significantly lower than those of the patients after illness or even after 1 month. In the patient group the mean value of entilation olume was significantly higher in those patients suffering pneumonia than in the others ($p < 0.01$ on the 49 watt-load)

Oxygen uptake was significantly lower in both patients after illness and control subjects after bed rest than after three months, the one month alues being intermediate There was a tendency for the patients to consume less oxygen than the control subjects, especiall on occasions I and II a difference which became significant when the oxygen consumption per kilogram body weight was calculated

In the patients, the entilatory coefficient (entilatory volume/oxygen uptake) was significantly higher on occasion I than on later occasions, a change not recorded in the control subjects, who had a lower entilatory coefficient than the pa tients on occasion I. After exclusion of those pa tients suffering from pneumonia the ventilatory coefficient was still significantly higher in the patient group than in th control group on the three lowest work loads ($p < 0.05$) Similarly the mean coefficient of the three pneumonia cases was higher than that of the other patients.

The respiratory exchange ratio (R) reached its highest values after illness, becoming less on later occasions. Some of these differences were significant. There was a tendency for the alues of the control group in most instances to be lower than *those of the patients on occasions I and II.*

Heart rates were higher in both patient and control groups after illness/bed rest than on later occasions, the differences being highly significant on the higher loads. As with R, a tendency existed for heart rates to be higher in the patient group than in the control group on occasions I and II The oxygen pulse was significantly lower on the first occasion than on later occasions in both patients and control subjects. The values for the patients were consistently lower than those for the control subjects, but not significantly so.

Discussion

In the studies referred to in chapt. 5 on influence of viral infection on the respiratory organs, signs of arterio-venous shunting (Berven 1962, Johanson *et al* 1969) and compliance changes (Picken *et al* 1972) were encountered. A shunting effect is also known to occur with immobilization (Berggren 1942, Ray *et al* 1974) and is believed to be due to fluid shifts in the lung parenchyma (Ray *et al* 1974). However the patients of Johanson *et al* (1969), suffering upper respiratory infection, were ambulant and therefore the authors attributed the recorded alterations to viral invasion of the lower respiratory tract, a documented occurrence in these illnesses (Burch *et al* 1961).

In the present study the differences in respiratory rate pulmonary ventilation and ventilatory coefficient during exercise between patients and control subjects might be explained in these terms, the mean difference being abolished after about 3 months (on occasion III)

The significant difference in oxygen uptake during exercise in both patients and control subjects on occasion I (after illness bed rest) when compared to later occasions might be explained by a shift in the metabolism in the direction of an increased carbohydrate utilization known to require less oxygen (Åstrand & Rodahl 1970) which, when more pronounced, influences R values significantly (Christensen & Hansen 1939).

In part of the present study group (seven patients and eight control subjects) the activities of two glycolytic and two oxidative enzymes were measured (Åström *et al* 1976, A) in biopsies from the quadriceps muscle Inter alia decreased activities of citrate synthetase were found both in the patients after illness and in the control subjects after bed rest, the activity being significantly lower in the patients. This finding might be associated with the difference in oxygen uptake recorded in the present study

Previous bed rest studies have reported some reduction (Taylor *et al* 1949 Birkhead *et al* 1963) or no significant change (Saltin *et al* 1968 A) in oxygen uptake on submaximal work loads.

Saltin *et al* (1968 A) found no alternation of ventilatory coefficient after bed rest. Berven (1962), on the other hand recorded a higher mean coefficient for a given mean work load in his pneumonia patients than in control subjects suffering other infections. Accordingly in the present study the mean ventilatory coefficient calculated after exclusion of the pneumonia cases, was lower than that of the pneumonia patients on all three work loads on occasion I. However the mean value for the non-pneumonia patients was significantly higher than that for the control group, a finding which, as stated above, supports a direct pulmonary influence of these infections.

The reductions in oxygen pulse recorded in both patient and control series agree with a deterioration in circulatory adjustment. As the present study did not include determinations of cardiac output it cannot be stated whether a hyper hypo- or normokinetic circulation (Hess 1948) predominated in these illnesses. In hepatitis A Lundbergh & Strandell (1974) found cardiac output to be enhanced at rest as a result of increased hepatic blood flow but no determinations during exercise were reported. Previous studies in normal subjects have revealed variable effects on cardiac output during exercise after bed rest. Thus, during supine submaximal work, two of the four subjects of Birkhead *et al* (1963) showed increased cardiac output whilst in the other two it changed in the opposite direction Saltin *et al* (1968 A) found reductions in cardiac output with both supine and upright exercise

Chapter 9
LACTATE PRODUCTION

Subjects and procedures

All series of subjects (chapt.) were included and th procedures detailed in chapt 3 were followed

Measurements

In connection with the exercise tests on the bicycle ergometer (chapt. 6) blood was sampled from the finger tip after arterialization by holding the hand in water of 45°C for a few minutes On the first occasion of measurements, a blood sample was taken within 2 minutes after the end of the exercise test, in series M and F while on succeeding occasions, the sample was taken when the subject had performed the same absolute amount of work as on occasion I In series C the sample was always taken in the 5th minute of work on the fourth load (196 watts). On 4 occasions the subject could not perform that amount of work and the lactate values from these occasions were therefore omitted in the calculations. The blood sample was divided into two subsamples, each analysed in duplicate.

According to Strandell (1964) there is an approximately linear relationship between the logarithm of the blood lactate concentration and the heart rate Consequently linear relationships should exist between log lactate and work load, although the regression lines should ha e different equations (slopes) depending on the working capacity The method of relating the physical working capacity to a given lactate concentration blood (W_{lact}) was introduced by Renck (1969) using at least one observed lactate alue and assuming an approximately constant resting value (Carlsson & Pernow 1959). Since in the present study lactate was always sampled, in each subject, t the same individual intensity of work on all occasions, the aforementioned relationships made it possible to calculate working capacity expressed a a percentage of a given lactate concentration (arbitrarily chosen but w thin the range of the observed alues) without assuming resting alue and despite the fact that only a single lactate alue was available for each exercise test (Fig 3)

Results

The blood lactate concentrations recorded are shown in Table XXI

After the same amount of work blood lactate levels were significantly higher after illness/bed rest (occasion I) then on succeeding occasions. In the patients, there was also a tendency for higher alues on occasion II as compared to occasion III, although this was not significant except in the female patients

In Table VIII the individually calculated W_{lact} alues are included expressed as fractions of the alues on occasion III Thus, on occasion I W_{lact} was 83 9 per cent in the male patients and 78 8 per cent in the female patients of the alues recorded on occasion III, a difference which was significant for both sexes There were no significant differences between the alues of occasions II and III In the control subjects, the reduction in W_{lact} was less pronounced than in the patients, but not significantly so when compared to the male patients, although a propably significant difference was noted on comparison with the female patients.

For comparison, individual calculations of W_{130} as fractions of the alues of occasion III were performed in addition, and are included in Table VIII Levels of significance of differences between occasions in W_{130} fractions are not indicated in the table, since they were the same as those of the absolute differences in W_{130} presented in Table XIV However individual differences between the

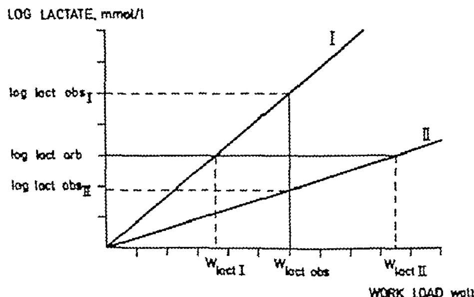


Fig 3 Schematic representation of relationships between log lactate and work load, measured on two different occasions, corresponding to different physical working capacities (I = lower II = higher) Log lact obs$_I$ and $_{II}$ denote the logarithms of the lactate values observed on each occasion fter a given amount of work performed ($W_{lact\ obs}$). $W_{lact\ I}$ and $_{II}$ denote the physical working capa-) on each occasion at an arbitrarily chosen lactate level ($lact_{arb}$)

$$\frac{lact\ I}{W_{lact\ II}} = \frac{\log lact_{II}}{\log lact_{I}}$$

Table III Individually calculated percentages (%) of W_{lact} values of occasion III, set to 100 per cent. For comparison means of corresponding percentages (%) of W_{sa} are indicated to the left in each column. (Means for column III = 100 % omitted)

	I				II				III		IV/0			
	W_{sa}		W_{lact}		W_{sa}		W_{lact}		W_{sa}	W_{lact}	W_{sa}		W_{lact}	
Series	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$	N	$\bar{x}$	N	N	N	$\bar{x}$	N	$\bar{x}$	N
M	83.4 NS	31	83.9 NS	[illegible]	[illegible]	6	[illegible]	[illegible]	31	26	103.1 NS	6	NS 108.5 NS	22
C	89.5	[illegible]	NS 95.0		103.[illegible]	[illegible]	[illegible]		[illegible]	21	97.4 NS	[illegible]	113.8 NS	20
F	75.3 NS	27	78.8 NS		87.4	[illegible]	[illegible]		[illegible]	[illegible]	97.9 NS	27	NS 106.1 NS	20

fractions of W_{lact} and those of W_{150} were calculated and tested for each occasion but no significant differences between these fractions were found on any occasion of measurements except for the control subjects on occasion 0 who showed higher W_{lact} values than W_{150} values ($p < 0.05$).

No significant differences were found between the group means of the W_{lact} fractions of the male patients when compared to the control subjects on any occasion of measurements, while such a difference was noted between the female patients and the control subjects both on occasions I and II. The same pattern was found in W_{150} fractions.

Discussion

The blood lactate levels recorded followed a pattern known from numerous previous studies showing higher levels at work rates corresponding to higher degrees of exhaustion (Holmgren & Ström 1959). In seven of the patients and eight of the control subjects of the present study a lower activity of total lactate dehydrogenase (LDH) was measured (as V_{max}, optimal rate of reaction) on occasion I than on later occasions (Åström *et al* 1976 A). This may seem contradictory but might be explained, firstly by the fact that total LDH was measured and no isoenzymes (Karlsson *et al* 1974 A) and, secondly by the recently decribed phenomenon of product inhibition resulting in a discrepancy between $\dot{V}_{max}$-values and the speed of the reaction in the tissues (Karlsson *et al* 1974 B).

In order to elucidate whether the deterioration in physical working capacity expressed in metabolic terms (W_{lact}) was of the same order of magnitude as that expressed in circulatory terms (W_{150}), the individual fractions of these variables were calculated for each occasion of measurements (Table VIII). The significant difference between the fractions found in the control subjects on occasion 0 is an illustration of the discrepancy between the circulatory and metabolic responses to temporary apprehension (occasion 0 was the control subjects first maximal exercise test). On the other occasions, no significant differences were recorded between the values of these two variables.

Chapter 10
ECG FINDINGS

Subjects and procedure

All subjects (chapt. 2) were included and the procedures detailed in chapt. 3 were followed.

Measurements

ECGs were recorded as described in chapt. 3 during rest in the supine position continuously during orthostasis and during exercise for detection of arrhythmia. Further recordings were made during supine rest at the end of standing and in the 5th minute of each work load immediately after completion of work, and at intervals of 4 3 10 minutes thereafter for inspection of the interval and T wave

The ECGs were analyzed to detect arrhythmias. On examination special attention was paid to the precordial leads for detection of possible abnormalities of the ST interval and T wave suggesting myocardial involvement (Bengtsson 1957 A). The ECGs were then classified on the basis of the appearance of the ST interval and T wave according to Holmgren *et al* (1959), along a four-grade scale code 1 representing discrete but definite changes.

Results

Arrhythmias did not occur except as premature beats Atrial premature beats and single monoform ventricular premature beats were recorded occasionally In two of the control subjects, premature beats of e ther type were recorded before or after exercise or during exercise on the lower loads, and occasionally on th higher loads There was no tendency for prematu e beat to be more common on occasion I than on later occasions in either patients or control subject

In one case ECG changes suggestive of myocarditis (Bengtsson 1957 B) pre ed during exercise and this patient was excluded completely from the study

The results of the evaluation of the ST interval and T wave are shown in Table XXII. Thus, significantly more pronounced changes of a sympathicotonic type were recorded after illness/bed rest (occasion I) than on later occasions. The control subjects showed somewhat higher mean values than the patients.

Discussion

Premature contractions are considered to be common in connection with various stress conditions, such as tobacco consumption or lack of sleep (Kay 1971) and atrial and ventricular premature contractions have been found more often in connection with upper respiratory infections than under normal conditions (B Ekblom, personal communic tion) Bengtsson (1957 A) found premature beats to occur at rest in about 10 per cent in his study of patients with abnormalities in their ECGs during acute infectious diseases. From the present study it cannot be stated that premature beats were more common after illness than on later occasions. Possibly premature beats might be more apt to occur in the early viraemic or febrile stage of illness than after subsidence of fever However there appear to be no controlled studies with continuous ECG recordings over hours or days reported in patients suffering acute infections.

Bengtsson (1957 B) states that the occurrence of isolated entricular premature beats during or afte exercise should not be judged to be abnormal On the other hand, Bengtsson (1957 B) found cases w th premature beats to ha e a higher incidence of changes in the exercise ECG than cases without such beats

The somewhat higher mean alues of the summed ECG diagnosis in the control subjects

than in the patients is explained by the fact that the former performed maximal work. The average degree of alteration was low when compared with findings reported in cases suffering from vasoregulatory asthenia (Holmgren *et al* 1959 Levander Lindgren 196).

Thus, in the present series, the lack of ECG changes suggestive of myocarditis during rest, orthostasis or exercise (except in one case, see above) is probably due to the selection criteria applied (chapt.)

Chapter 11
GENERAL SUMMARY

The effects of acute infectious disease on physical fitness were investigated in 47 male and 33 female patients (mean age 25.8 and 26.1 years, respectively) hospitalized with various acute infectious diseases without cardiac complications. Twenty two healthy men (mean age 25.0 years), confined to bed for the same period of time as the patients, served as a control group. The aims were to try to establish the extent and duration of physical deterioration caused by illness/bed rest 1) as evaluated by history and clinical signs, 2) as measured as reaction to upright exercise on the bicycle ergometer with determination of oxygen uptake and lactate production and measurement of the heart volume on X ray and 3) as measured as reaction to standing (orthostasis). Further findings in patients and control subjects were compared in an attempt to evaluate the relative effects of bed rest and illness.

Apart from routine clinical procedures measurements were performed on four occasions: directly after illness/bed rest (occasion I) after about 1 month (occasion II) after about 3½ months (occasion III) and about 1 year after illness in the patients (occasion IV) or in the control subjects, 1 week prior to bed rest (occasion 0). Measurements of occasion III were used to represent the subject's habitual level (= reference level). Measurements of occasion IV were performed to establish possible clinical sequelae and, additionally — since such sequelae were not apparant — to control the relevance of the measurements performed on occasion III. Findings on occasion III and IV were usually similar.

The results indicated that clinical symptoms or signs possibly referable to circulatory dysfunction were present in 69 per cent of the patients 1 month after illness, while 3 months after illness, only one patient suffered general tiredness.

In the male patients after illness, physical working capacity expressed as work load at heart rate 150 beats/min (W_{150}) was 79.3 per cent of that of occasion III while in the female patients it was 72.7 per cent of their reference level. The deterioration was, in relative terms, significantly more pronounced in the female patients. The control subjects deteriorated to 86.9 per cent of their reference level as a result of bed rest. Except in those patients suffering pneumonia, there was no statistical difference in amount of deterioration, either in relative or absolute terms, between male patients and control subjects although on average, a tendency existed for the male patients to show a higher degree of deterioration in physical working capacity. In the patients, the deterioration in maximal work performed ($W_{max\ perf}$) roughly followed that of W_{150}. Except in male patients suffering pneumonia, whose W_{150} values were *lower no significant differences referable to diagnosis or aetiology* were found. Change in pulse related physical working capacity from occasion I to III showed highly significant correlations to the duration of bed rest, while correlations to duration of illness or fever were lower. *Multiple correlation analysis indicated bed rest to be the* most important factor.

The reaction to orthostasis, measured as maximal heart rate (HR) and mean HR during 8 minutes standing, was not significantly altered by bed rest alone but highly significant differences of 18.5 — [illegible] 1 beats per minute were encountered in the patients when recordings on occasion I were compared to recordings on occasion III. In the female patients the systolic blood pressure (BP lowest and mean) during standing was similar on occasions I and III while the male patients showed a significant decrease after illness. The *standing diastolic BP was significantly lower after*

illness/bed rest in the male patients and control subjects but not in the female patients who maintained the same level.

The orthostatic dysfunction expressed in terms of HR response, was significantly more pronounced in those patients who suffered from pneumonia than in the other patients.

Respiratory rate and ventilation volume tended *to be higher on occasion* I *than on succeeding* occasions, but bed rest alone had no effect on these variables. For the same absolute amount of work, oxygen uptake was lower on occasion I than on occasion III, most differences being probably significant.

The blood lactate concentration, determined after the same absolute amount of work, was significantly higher on occasion *I than on succeeding* occasions in both patients and control subjects. An inverse pattern was seen when the working capacity was expressed as percentages of the values of *occasion III and related to a given lactate level* (W_{lact}). On occasions I and II both the W_{lact} fraction and the W_{130} fraction of the female patients were significantly lower than those of the control subjects, indicating a greater relative deterioration in the female patients. Similarly these values were lower in the male patients than in the control subjects, but not significantly so. There were no significant differences in the W_{lact} fraction when compared to the W_{130} fraction on occasions I or II, in each series of subjects, indicating that the deterioration was roughly parallel when expressed in circulatory or in metabolic terms.

In conclusion, the results confirm that cardiovascular dysfunction occurs in patients confined to bed with acute febrile infections. Part of the deterioration is caused by the clinical bed rest but it is relevant to conclude that acute febrile infection as such brings about an additional impairment. Thus, in the present study with bed rest effects eliminated, orthostatic dysfunction has *been shown to occur. On the other hand, the* physical working capacity expressed in different terms, was not significantly reduced by illness as such (except in pneumonia patients) although a *consistent trend suggesting an additional effect* added to that caused by bed rest alone was demonstrated. Heart volume was not significantly altered.

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TABLES

Table IX Anthropometric data and heart volume in patients and control subjects.

	I			II			III			IV/0		
	$\bar{x}$	SD	N	$\bar{x}$	SD	N	$\bar{x}$	SD	N	$\bar{x}$	SD	N
Body height, cm												
Series M	180 1	7.2	44									
	NS											
C	179.5	5.2	22									
F	166.2	6.3	33									
Body weight, kg												
Series M	71 9	12.3	44	73 6	13.6	34	75.8	13 4	28	78.2	14.5	27
	NS			NS			NS			NS		
C	70 9	9 7	22	71.5 NS	9 8	22	72.0	10.5	22	NS 72.2	10.[illegible]	[illegible]2
F	57.2 NS	7.5	32	57 1 NS	7 4	23	59.0	6 6	27	NS 58 9	7.5	28
Heart volume ml												
Series M	NS 808 9 NS	163 1	27	781 0 NS	132.8	26	806.0	144 7	27	NS 822.0 NS	169.8	27
				NS								
C	NS 699 9 NS	92.8	22	724.3 NS	116.2	22	713.6	137 1	22	NS 718 4 NS	123 9	[illegible]2
F	NS 5[illegible]7.2 NS	71 9	30	525 4 NS	67 4	27	539 9	67 0	25	NS 538 0 NS	72.4	[illegible]7

Table X Resting heart rate and systolic and diastolic blood pressures (BP) in patients and control subjects.

	I			II			III			IV/0		
	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N
Resting heart rate *beats/min*												
Series M	NS 72.7^{NS} NS	11.8	47	70.4^{NS} NS	10.4	38	68.6 NS	9 7	31	NS 65.9^{NS}	9.9	27
C	NS 73 9^{NS} NS	15 1	22	73 0^{NS} NS	10.0	22	75 4 NS	16.2	22	NS 75.5^{NS} NS	13 4	22
F	79.3	11 0	33	74.2^{NS} NS	12.3	29	71 9 NS	11.2	28	NS 71.3 NS	10 6	30
Resting systolic BP *mm Hg*												
Series M	125 1^{NS} NS	12.3	47	125.3^{NS} NS	13.2	38	127 4 NS	19.2	31	NS 121.8^{NS} NS	10.1	27
C	NS 124 1^{NS}	10.4	22	123 9^{NS}	9.5	22	122.0	9.0	22	NS 121.9^{NS}	8.7	22
F	NS 117.0^{NS}	11.7	33	114 7^{NS}	10 1	29	115 4	10.2	28	NS 115.3^{NS}	11.8	30
Resting diastolic BP *mm Hg*												
Series M	NS 65 7^{NS}	11 1	47	67 7^{NS}	12.2	39	66.6	15 4	31	NS 65.0^{NS}	10.5	27
C	NS 57.5^{NS}	9 6	22	56 6^{NS}	8 4	22	56.4	9.2	22	NS 57.5^{NS}	7 7	22
F	NS 69 7^{NS} NS	8.9	33	67 9^{NS} NS	12.4	29	70.0 NS	12.2	28	65.2 NS	11 1	30

Table XI Respiratory rate at rest, peak expiratory flow rate, and haemoglobin concentration in patients and control subjects.

	I			II			III			IV/0		
	$\bar{x}$	SD	N	$\bar{x}$	SD	N	$\bar{x}$	SD	N	$\bar{x}$	SD	N
Respiratory rate *breaths/min*												
Series M	NS 16.7 NS	4.1	45	17.4 NS	3.6	37	16.5	2.7	31	NS 17.0 NS	3.5	26
	NS			NS			NS			NS		
C	NS 16.4 NS	2.7	[illegible]2	16.5 NS	2.8	21	17.3	2.9	22	15.5 NS	3.6	2[illegible]
	NS			NS			NS			NS		
F	NS 17.1 NS	3.6	33	16.3 NS	3.3	29	16.3	3.6	28	NS 16.3 NS	2.6	30
	NS			NS			NS			NS		
Peak expiratory flow *litres/min*												
Series M	NS 551.2	78.0	43	573.1 NS	79.8	36	554.3	68.3	28	NS 563.4	84.0	6
	NS			NS			NS			NS		
C	NS 547.0 NS	51.7	22	540.9 NS	53.2	2[illegible]	550.7	47.4	[illegible]1	NS 543.6 NS	48.7	22
F	409.8	39.3	32	444.6 NS	40.0	26	458.0	80.0	27	NS 443.8	39.7	26
Hb *g/litre*												
Series M	139.5 NS	13.9	46	142.6	11.9	34	149.5	9.8	27	NS 150.6	9.1	23
				NS			NS			NS		
C	NS 149.1 NS	8.1	22	146.4 NS	8.4	22	147.3	8.2	22	NS 148.0 NS	9.4	22
F	127.2 NS	9.2	23	130.2 NS	9.2	26	134.0	10.7	26	129.5 NS	9.7	24

Table XII Duration of illness (DI) fever (DF), and bed rest (DB) in patients and in different diagnosis groups (D-groups) of the patients. D-groups: AD = all diagnoses, VM = viral or mycoplasma infection, B = bacterial infection, ME = meningoencephalitis, VM ME = viral and mycoplasma infection except meningoencephalitis, P = pneumonia, AD-P = all diagnoses except pneumonia.

	N	DI $\bar{x}$	DI SD	DF $\bar{x}$	DF SD	DB $\bar{x}$	DB SD
Total series (AD)							
M	47	10 7	6 2	7 9	4 9	8 4	4.2
		NS		NS			
F	33	8 1	5.6	6.5	4 1	6.5	4 0
Series M							
D-group VM	42	11.3	5.9	8 4	4 9	8 7	4.2
B	5	3.8	1 1	3.8	1 1	3.8	1.3
ME	18	8.2	3.0	7.6	2.5	7 7	3 1
				NS		NS	
VM ME	24	13.8	6.6	9.0	6.0	9.8	4 6
P	8	11 1	5 6	10.8	5 1	10.6	5.9
		NS		NS		NS	
AD-P	39	10.6	6.4	7 4	4 7	7 9	3.8
Series F							
D-group VM	25	7.2	4 1	6.2	3 4	6.5	3.5
		NS		NS		NS	
B	8	10 9	8.6	7.5	6.0	6.4	5 4
ME	8	4.5	1 4	4.5	1 4	5 1	3.2
				NS		NS	
VM ME	17	8 4	4 4	7 1	3.8	7.2	3 6
P	8	8 4	3 4	8 1	3.5	7.8	4 7
		NS		NS		NS	
AD-P	25	8.0	6.2	6 0	4.2	6 1	3 7
Series M + F							
D-group VM	67	9.8	5 7	7 6	4.5	7.9	4 1
		NS		NS			
B	13	8.2	7.5	6 1	5 0	5 4	4 4
ME	26	7.0	3 1	6 6	2.7	6 9	3.3
				NS		NS	
VM ME	41	11.6	6.3	8.2	5.3	8.7	4 4
P	16	9.8	4 7	9 4	4 4	9.2	5 4
		NS				NS	
AD-P	64	9.6	6 4	6.8	4.5	7.2	3.8

Table XIII Dominating symptom and degrees of exhaustion at exercise tests presented as the percentage of subjects, on each occasion indicating a particular symptom and one of three degrees of exhaustion (code 1 = additional work possible for > 3 code 2 = about 2, code 3 = < 1 min)

		I		II		III		IV/0	
		%	N	%	N	%	N	%	N
Dominating symptom at work									
Series M	Headache/dizziness/nausea	4.5	2	0 0	0	0.0	0	0 0	0
	Shortness of breath	31.8	14	24.3	9	16.1	5	14.8	4
	Tiredness of legs	38 6	17	59.5	22	58 1	18	55.6	15
	General tiredness	15.9	7	13.5	5	19 4	6	25 9	7
	No symptom	9 1	4	2.7	1	6.5	2	3 7	1
C	Headache/dizziness/nausea	0 0	0	0 0	0	0 0	0	0.0	0
	Shortness of breath	54.5	12	27.3	6	14.3	3	45.5	10
	Tiredness of legs	31.8	7	40 9	9	42.9	9	40 9	9
	General tiredness	13 6	3	31.8	7	42.9	9	13 6	3
	No symptom	0.0	0	0 0	0	0 0	0	0.0	0
F	Headache/dizziness/nausea	24.2	8	3.5	1	3 6	1	0.0	0
	Shortness of breath	24.2	8	6 9	2	10 7	3	17.2	5
	Tiredness of legs	21.2	7	44.8	13	39.3	11	37 9	11
	General tiredness	18.2	6	27.6	8	25.0	7	44.8	13
	No symptom	12.1	4	17.2	5	21 4	6	0.0	0
Degree of exhaustion									
Series M	Rating Code 1	18.2	8	16.2	6	19 4	6	11 1	3
	2	40 9	18	59.5	22	61.3	19	59.3	16
	3	40.9	18	24.3	9	19 4	6	29 6	8
C	1								
	2								
	3	100	22	100	22	100	21	100	22
F	1	15.2	5	17.2	5	28.6	8	10.3	3
	2	48.5	16	65.5	19	53 6	15	75.9	22
	3	36.4	12	17.2	5	17 9	5	13.8	4

Table XIV Physical working capacity (W_{HR} and $W_{max\ perf}$) in patients and in control subjects.

	I			II			III			IV/0		
	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N	$\bar{X}$	SD	N
W [illegible]												
Series M	84 4	29.5	43	100.3	25 0	37	109.9	25.3	31	NS 117 7	27.2	27
	NS			NS			NS					
C	89.5	24.5	22	106.0 NS	28.0	22	107.0	38.1	21	NS 99.3	26.9	22
F	45.3	18.3	31	60.2	18.5	29	73.6	18 7	28	NS 69 0	20 1	30
W [illegible]												
Series M	115 0	33.6	44	134.2	28.5	37	145.0	29 7	31	NS 149.9	29.9	27
	NS			NS			NS			NS		
C	125.2	21 1	22	144.3 NS	27.8	22	144 0	32.9	21	NS 136.0	28.9	22
F	72.9	22.1	32	83.7	20.6	29	100.3	22.2	28	NS 94 4	22.7	30
W [illegible]												
Series M2	148.8	30.2	12	161 1	28.3	12	174.5	32.1	12	NS 175 4	32.2	12
	NS						NS			NS		
C	165.2	23.0	22	183.9 NS	29.5	22	182.5	33.2	21	NS 176.1	31 1	22
Wmax perf												
Series M	133.5	46.6	36	161.2 NS	46.9	31	172.9	38 4	25	NS 187.5	35 0	24
C	224.6	27.6	22	235.9 NS	30 7	22	234.9	30 7	21	NS 233.2	32.8	22
F	79 0	18.9	28	96.2	15.9	24	107.3	14.2	20	NS 111 9	21.2	26

Table XVII Correlations of some variables of physical working capacity and orthostatic tolerance to duration of illness (DI) fever (DF), and bed rest (DB) and to reference levels (W_{III} HR_{III}) of variables. Roman numerals refer to occasions of measurements.

Variable	Series M				Series F				Series C
	DI	DF	DB	Corresponding W_{III} HR_{III}	DI	DF	DB	Corresponding W_{III} HR_{III}	Corresponding W_{III} HR_{III}
ΔW_{130} III—I	0.40	0.33	0.58	0.30	0.32	0.40	0.61	0.57	0.27
ΔW_{150} III—I	0.43	0.36	0.62	0.23	0.53	0.58	0.58	0.46	0.07
ΔW_{170} III—I (M2)	0.53	0.42	0.74	0.45	—	—	—	—	0.06
ΔWmax perf III—I	0.08	0.15	0.24	0.21	0.08	0.09	0.43	0.48	—0.15
ΔHR_{max} during standing I—III	0.36	0.46	0.64	—0.28	0.36	0.49	0.42	—0.17	—0.34

Table XVIII Highest attained heart rate (HR) during 8 min standing (HR_{max}) mean HR, mean systolic blood pressure (BP) mean diastolic BP and lowest pulse pressure during standing in patients and control subjects.

	I			II			III			IV/0		
	X̄	SD	N	X̄	SD	N	X̄	SD	N	X̄	SD	N
HR_{max}												
Series M	107 1 NS	17.5	47	92.7 NS	13 1	38	88 4	10 9	31	NS 87.9	11.9	26
C	NS 100.6 NS	17 7	22	94.9 NS NS	13.8	22	99.6	15.2	22	NS 96 1 NS NS	15.9	22
F	112.2 NS	18 1	33	97 1 NS NS	15 7	29	90 1 NS	13 7	28	NS 92.0 NS	17.3	30
Mean HR												
Series M	103 0 NS	17.0	42	88.6 NS	13 1	38	84.5	11 4	31	NS 84.0	11 7	26
C	NS 96.1 NS	17.2	22	91 1 NS NS	14 1	22	95.2 NS	15.3	22	NS 92.9 NS NS	15 9	22
F	106.7 NS	18.4	33	92.5 NS NS	15 1	29	87 0 NS	13.6	28	NS 87 4 NS	16 9	30
Mean systolic BP												
Series M	114 4	15 0	41	122 4 NS NS	12.8	36	123.3 NS	19 4	31	NS 122.5 NS	12.4	26
C	NS 122.7 NS	9 1	22	123.5 NS	10 1	22	123.5	8.5	22	NS 121 1 NS	10.0	22
F	NS 110 7 NS NS	14 7	33	112.4 NS	11.0	28	113.2	9 1	28	NS 112.0 NS	12.0	30
Mean diastolic BP												
Series M	NS 75.0 NS	12.1	41	80.3 NS NS	13.0	37	79.0 NS	16.5	30	NS 79.9 NS NS	10.8	26
C	70.5 NS	9 9	22	74 4 NS NS	9.3	22	76.5 NS	8.1	22	NS 74.5 NS NS	6.9	22
F	NS 76 5 NS NS	10 4	31	76.3 NS NS	11.2	28	77.5 NS	10.7	28	73 9 NS	7 4	30
Lowest pulse pressure												
Series M	33.5 NS	13 4	40	35 4 NS NS	8.3	36	37 8 NS	14.0	30	NS 36.2 NS	8.3	26
C	46 4	11.9	22	40 9 NS	14 1	22	38.2	15 7	22	NS 40.2	13.1	22
F	NS 27.0 NS NS	13 1	31	29.6 NS	10.4	28	29.3	8 4	[illegible]8	NS 30.8 NS	11 0	30

Table XIX Differences in HR_{max} (ΔHR_{max}) mean HR (Δ mean HR), mean systolic BP (Δ systolic BP) and mean diastolic BP (Δ mean diastolic BP) between different occasions in patients and control subjects.

Measurements during standing	III—I			III—II			II—I			III—IV/0		
	$\bar{d}$	SD_d	N	$\bar{d}$	SD_d	N	$\bar{d}$	SD_d	N	$\bar{d}$	SD_d	N
ΔHR_{max}												
Series M	—15.4	16.3	31	—4.0	9.5	26	—13.9	15.0	37	1.3 NS	9.4	25
C	— 1.0	15.5	22	4.7	12.6	22	— 5.7	13.3	22	3.5 NS	10.9	22
F	—23.0 NS	16.0	28	—4.9 NS	14.2	24	—16.9 NS	18.7	29	—3.0 NS	13.1	27
ΔMean HR												
Series M	—14.6	16.7	28	—4.0	9.2	25	—14.0	14.2	35	—0.7 NS	9.1	23
C	— 0.9	15.5	22	4.0	13.8	22	— 5.0	13.0	22	—2.3 NS	10.9	22
F	—21.9 NS	16.5	27	—4.2 NS	12.9	23	—16.0 NS	17.9	29	2.3 NS	12.3	25
ΔMean systolic BP												
Series M	10.2	16.2	27	2.9 NS	12.3	24	8.1	13.5	34	0.8 NS	12.9	24
C	0.9 NS	7.9	22	0.1 NS	7.7	22	0.8 NS	6.9	22	2.4 NS	7.8	22
F	4.4 NS	13.0	28	—0.7 NS	10.0	23	2.2 NS	10.7	28	1.9 NS	10.0	27
ΔMean diastolic BP												
Series M	1.4 NS	13.0	26	—1.7 NS	7.9	24	5.3 NS	10.5	35	—0.8 NS	12.5	24
C	6.0 NS	9.1	22	2.1 NS	6.6	22	3.9 NS	9.2	22	1.9 NS	7.0	22
F	1.7 NS	10.7	26	1.4 NS	11.2	23	— 0.6	10.4	26	4.0 NS	8.7	27

Table XX Data from exercise tests on three loads in patients (series *M2*) and control subjects (series C). V_E = pulmonary ventilation, V_{O_2} = oxygen uptake, V_E/V_{O_2} = respiratory coefficient, and R = respiratory exchange ratio.

49 watts	Series	I $\bar{x}$	SD	N	II $\bar{x}$	SD	N	III $\bar{x}$	SD	N	IV/0 $\bar{x}$	SD	N
Respiratory rate *breaths/min*	M2	NS 20.9 NS	3.9	12	18.7 NS	4.2	12	18.5	4.4	12	NS 17.5	4.3	12
					NS			NS			NS		
	C	NS 17.0 NS	2.8	21	17.6 NS	2.8	22	16.8	3.5	21	NS 17.2 NS	3.6	22
V_E *l x min⁻¹ STPD*	M2	22.7 NS	3.2	12	21.1 NS	3.5	12	19.9	2.2	12	NS 20.3	2.1	12
					NS			NS			NS		
	C	NS 20.2 NS	2.5	22	19.8 NS	2.5	21	20.4	3.0	21	NS 20.2 NS	2.9	22
V_{O_2} *l x min⁻¹ STPD*	M2	0.89 NS	0.11	12	0.95 NS	0.12	12	0.97	0.08	12	NS 1.00	0.08	11
		NS			NS			NS			NS		
	C	0.93 NS	0.10	22	0.96 NS	0.10	21	1.00	0.08	21	NS 0.98 NS	0.12	22
V_E/V_{O_2}	M2	25.8	5.4	12	22.5	3.9	12	20.5	2.2	12	NS 20.1	2.1	11
					NS			NS			NS		
	C	21.7 NS	2.3	22	20.7 NS	2.2	21	20.5	2.7	21	NS 21.0	2.9	22
V_{O_2} *ml x kg⁻¹ x min⁻¹ STPD*	M2	NS 11.7 NS	1.6	11	12.5 NS	1.4	11	12.6	1.3	11	NS 12.3 NS	1.6	11
					NS						NS		
	C	NS 13.3 NS	1.7	22	13.5 NS	1.8	21	14.0	1.8	21	NS 13.8 NS	2.2	22
R	M2	0.93	0.07	12	0.86 NS	0.06	12	0.86	0.04	12	0.60	0.08	11
		NS			NS			NS					
	C	0.91	0.07	22	0.87 NS	0.07	21	0.86	0.04	21	NS 0.87 NS	0.07	22
Heart rate *beats/min*	M2	107.4 NS	16.4	12	101.4 NS	13.2	12	96.9	11.3	12	NS 94.9	11.7	12
		NS			NS			NS					
	C	NS 105.5 NS	14.4	22	101.7 NS	11.8	22	101.0	15.7	21	NS 104.1 NS	12.7	22
Oxygen pulse *ml/heart beat*	M2	8.5	1.7	12	9.2	1.8	12	10.2	1.3	12	NS 10.9	1.2	11
		NS			NS			NS					
	C	9.0	1.2	22	9.4 NS	1.2	21	10.1	1.6	21	NS 9.5 NS	1.4	22

98 watts	Series	I $\bar{x}$	SD	N	II $\bar{x}$	SD	N	III $\bar{x}$	SD	N	IV '0 $\bar{x}$	SD	N
Respiratory rate *breaths/min*	M2	NS 23 7 NS	4 4	12	21.8 NS	5.3	11	21 0	4.6	12	NS 19.5	3.9	12
	C	NS 18.5 NS	3 0	22	19 0 NS	2.7	22	NS 18.6	3 1	20	NS NS 18.7 NS	4.1	22
V_E *l x min⁻ STPD*	M2	NS 34.3	7 0	12	31 4 NS	5.3	12	30 4	4 7	12	NS 30 9 NS	4 0	12
	C	NS 29 7 NS	3 1	22	NS 28.8	4.0	22	NS 30 7	4.2	19	NS NS 29 7 NS	3.8	22
V_{O_2} *l x min⁻ STPD*	M2	1.38 NS	0 16	12	1 42 NS	0 13	12	1 48	0 11	12	NS 1.55	0 10	11
	C	NS 1 46 NS	0.10	22	NS 1 46 NS	0.14	22	NS 1.50	0 10	19	NS NS 1.50 NS	0 14	22
V_E/V_{O_2}	M2	25.2	6.0	12	22.2 NS	4 2	12	20.5	2.6	12	NS 19 6	1 8	11
	C	NS 20.5 NS	2.3	22	NS 19 9 NS	2.6	22	NS 20.5	2.6	19	NS NS 19.8	2.8	22
V_{O_2} *ml x kg⁻ x min⁻ STPD*	M2	NS 18 1 NS	ʟ3	11	18.6 NS	1.5	11	19 0	2.2	11	NS 19.0 NS	2.4	11
	C	NS 20.8 NS	2.5	22	20 7 NS	3 0	22	21 1	ʟ8	19	NS NS 21.2 NS	3.2	22
R	M2	0 97 NS	0 07	12	0.93 NS	0.08	12	0.92	0.05	12	0.87	0 04	11
	C	NS NS 0 93 NS	0 05	22	NS 0 91 NS	0 06	22	NS 0 93	0 04	19	NS NS 0 90	0 05	22
Heart rate *beats/min*	M2	138 0	19 0	12	130 1	16.4	12	121 9	16 6	12	NS 122.8	15 7	12
	C	NS 133 9	12.9	22	NS 1ʟ5 4 NS	12.3	22	NS 1ʟ5 8	15.2	21	NS NS 130 4 NS	14.6	22
Oxygen pulse *ml/heart beat*	M2	10.2	1 7	12	11 1	1.8	12	12.3	1 7	12	NS 13 0	1.8	11
	C	NS 11.0	1.2	22	NS 11 7 NS	1.6	22	NS 12.3	1 6	19	NS 11 7	1 6	22

147 watts	Series	I $\bar{x}$	SD	N	II $\bar{x}$	SD	N	III $\bar{x}$	SD	N	IV/0 $\bar{x}$	SD	N
Respiratory rate *breaths/min*	M2	NS 26.9 NS	3.8	10	26.3	6.1	12	23.9	4.8	12	21.8	4.7	12
	C	NS 1.6 NS	3.6	22	21.3 NS	2.9	22	NS 21.2	3.4	21	NS NS 21.0 NS	3.6	22
V_E *l x min⁻ STPD*	M2	NS 47.5 NS	9.3	10	47.1	8.3	12	44.6	7.9	12	NS 46.5 NS	7.3	12
	C	NS 42.1 NS	4.7	22	41.5 NS	4.6	22	NS 43.2	6.1	21	40.9 NS	4.9	22
V_{O_2} *l x min⁻ STPD*	M2	NS 1.93 NS	0.16	10	2.01 NS	0.15	12	2.06	0.13	12	2.16	0.13	11
	C	NS 2.02 NS	0.11	22	NS 2.06 NS	0.14	22	NS 2.10	0.14	21	2.04 NS	0.14	22
V_E/V_{O_2}	M2	24.9 NS	5.7	10	23.7 NS	3.1	1	21.6	3.2	12	NS 21.0 NS	2.5	11
	C	NS 20.8 NS	2.1	22	20.1 NS	1.9	22	NS 20.6	2.3	21	NS 19.8	2.0	22
V_{O_2} *ml x kg⁻ x min⁻ STPD*	M2	NS 3.5 NS	2.5	10	26.2 NS	2.0	11	26.5	3.1	11	NS 26.6 NS	3.9	11
	C	NS 28.9 NS	4.0	22	29.4 NS	4.4	22	79.3	3.9	21	NS NS 28.6 NS	3.9	22
R	M2	NS 1.0 NS	0.06	10	0.98 NS	0.08	12	0.98	0.05	12	0.94	0.05	11
	C	NS NS 0.97 NS	0.05	22	NS 0.95 NS	0.05	22	NS 0.96	0.04	21	NS NS 0.96 NS	0.06	22
Heart rate *beats/min*	M2	161.0 NS	12.9	9	159.6	15.2	11	151.6	15.5	11	NS 154.4 NS	17.2	12
	C	NS 162.6	11.3	22	NS 152.5 NS	13.1	22	NS 153.9	17.5	21	NS NS 156.2	15.0	22
Oxygen pulse *ml/heart beat*	M2	11.9	1.3	10	12.7 NS	1.9	12	13.5	1.7	12	NS 14.3	1.8	11
	C	NS 12.5	1.0	22	NS 13.6 NS	1.6	22	NS 14.0	1.8	21	NS 13.1	1.5	22

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Effects of Z
in Human Rec

By Sten James

Wiksell Periodical Company

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EFFECTS OF ZINC DEFICIENCY IN HUMAN REPRODUCTION

By

Sten Jameson

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DEFINITIONS

Duration of pregnancy   280 days from first day of last menstruation 40 weeks

Immatur infants = birth weights less than 2500 g

Dysmature infants   infants born post term in the 42nd week of gestation or later with clinical signs of postmaturity

ZINC AND COPPER IN PREGNANCY CORRELATIONS TO FETAL AND MATERNAL COMPLICATIONS

By

Sten Jameson

The rum zinc conce tration decre during human pregna cy (B r f tam 1952 Rothe 1960 Halsted 1968 Hüh 1972 Hambidge 1974) Contraceptive ste oids have a simila ffect (Halsted 1968)

It is not known whethe this decrease is pur ly physiological ff ct or an e pre ion of a defi i cy state implying isk to mother or child (Prasad 1970) It is p ssible that changes i zi c met bolism during human pregnancy are much more important tha we have thought (WHO 1973) Fe pregnancies have occu red in wome with acrodermatitis t opathic zi d fici ncy stat (Moynahan 1974); s vere f tal lformatio have been record d (on of ne cephaly Neldner 1974 on of achondropl tic dwarfis Epstei 1960 one sponta ous abortion and one infant with low birth weight have also been reported V rbu g 1974)

The po ibility f co relation betwe n hum n matern l i c defi iency a d conge ital malformations specially anomalies of the central nervou system h been di d (S ver 1973) but no s ch co ne ion has yet bee demonstr ted

In l boratory anim l pe ime t l zin deficiency re lts in educed f rtility a d the in ide ce of f t l malf rmations i raised (Blomberg 1960 Hu l y 1966 Swe erton 1969 Warkany 1973)

The ob rvation nd the disc very of DNA-polymera as zinc metalloprot i (Sl ter 1971) may imply th t DNA ynthesis i impaired in in defici cy (H ley 1972 Hs 1975) Whe i defi i ncy occu s it y well ffe t ll yst i hi h there i a rapid ll-turnover

DEFINITIONS

Duration of pregnancy 280 days from first day of last menstruation 40 weeks

Immature infants birth weights less than 2500 g

Dysmature infants infants born post term in the 42nd week of gestation or lat r with clinical signs of postmaturity

ocid f rrocya ide whi h give Prussian-blue reaction

The number of i tracellular ph gocytosed cells or amo t of cell debris in bone marrow macrophages wa registered accordi g to a semi quantitative scale 1 - 3 (V)

The ob tetricia s and paediat icians in ch ge of the pati ts had no knowledge of the r ult of the zinc a d copper stimation

Rel vant facts co cerning mother and infant were obtained from ca records: the duration of labour blood l duri g d livery th weight and maturity grade of the inf nt and any malformations were record d

Venous blood was obtai ed a d c ibed ab ve from 17 ppare tly healthy wome All wer of hild-be ring ge and none receivi g drugs or contraceptive ster ds Thes 17 wome constit t the o - mal controls

Mean value estimations Stud nt s t-test and regre sion an lysis were u d in the t ti tical alyse

All labo atory data r alcul ted to SI nits

R sult

All but one f 84 p imigravidae e amined i the 14th week of gestation howed haemogl bin conce trations ce di g 110 g/l (me 123 g/l range 109 - 149 g/l) See T bl 1

One woman howed n bnormally low vitami B 12 conce tration nd one lowe li it folat once tration No bone marrow haemosid rin was prese t i ithe and o disturba of cellmaturation ith megaloblast tra formation wa found See Tabl 1

F rty five of the gra idae (53 %) showed o bone marrow ha moside i or only t c amounts (tabl 2 which al o give the degre of intrac ll l r ll fragme t i bone marrow r phages)

Labour exceeded 30 hours in a f rther thre women and these ought properly to have bee cl ssed as cases of prolonged labour (Willson 1971) See Table 4

Two women d veloped complications d ring delivery (ruptured cervix and lacer ted perineum) See Table 4

In all 23 women showed complications duri g delivery and/or gave birth to immature infants These constitute Group B

Fifty nine women gave birth to normal infants by ormal delivery Zinc values are mis ing for 3 of them The remaining 56 women constitut Group A Compared to the normal Group A the 7 women who gave birth to imm ture infants showed significantly lower zinc concentrations d ring e rly pregnancy (p < 0 01)

Compared to Group A the 18 women with complication duri g labour showed significantly lower serum zi c d ring arly pregnancy (p < 0 001)

Compared to Group A Group B showed significantly lower zinc concen tr tio s d ring early pregnancy (p < 0 001) S Table 5

	mean	S D	n	t	p
Group A S-Zinc µmol/l	16 0	1 9	56		
Group B	13 9	2 0	23	4 49	< 0 001
Immature deliveries µmol/l	13 8	2 4	7	2 83	< 0 01
Ab ormal	13 9	2 0	18	4 23	< 0 001
G oup A S-c ppe µmol/l	35 6	6 9	54		
Group B	39 4	5 6	23	2 33	< 0 025

Table 5 Mean S-Zi c nd S copper co centr tion t first examination in the 14th we k of gestation The groups are defined in text Stud t t-t st as used to compare group A with other g o p

In contrast there were no significa t diff re ces betwee Groups A and B with regard to haemoglobin bo ma row ha mosid rin vitami B 12 or folate concentration

Concerning serum coppe o significa t diff r nces were fo d betw G oup A and 7 women with immature i fants or betw n Gro p A and 18 women with complication of labou The serum copper was significantly higher in Group B th n Group A (p < 0 025) See T bl 5

Among 79 women delivered and irrespective of clinical findings there is a significant differe ce in early pregna cy seru zi c between those in whom l bour e ceeded 20 hours and wome with normal l bour Compared to 63 wome with labour of less than 20 hour 16 women i hom l bour xceeded 20 hour howed signifi ntly lower rum zin during rly pregnancy (p < 0 05) The 7 women that gave birth to immature inf ts had hort l bour and these figures reduce the degree of signific ce (Tabl 6)

	Duration of l bour	< 10 h		10–20 h		> 20 h
Mean	S Zin µmol/l	15 5		15 8		14 4
S D		2 2		2 2		1 7
		32		31		16
t			0 55		2 11	
p			N S		< 0 05	

Table 6 M an ru i c co entratio in the 14th week of gest tion corrrel ted t d ration of l bour Compa ison between women with l bour < 10 h and labou 10–20 h and betwee wome with labour < 20 h and labou > 20 h

Twenty ix wome wer delivered in the 40th week of gest tion A di t ibution curve showing week f delivery correlated to th rum inc conce tration d ri g ea ly pregna cy is hown in Tabl 7 and Fig 3

	mean	S D	n	t	p
40th w k of gestation S-Zinc µmol/l	16 4	2 0	25		
39th week	15 6	1 9	8		
38th week	14 8	2 2	7		
41st week	16 1	1 9	11		
42nd week	15 0	1 9	14		
42nd-44th we ks	14 6	1 9	22	3 14	<0 005
35th-38th weeks	13 9	2 1	13	3 52	<0 005
43rd-44th weeks	13 9	1 9	8	3 03	<0 005
35th-37th weeks	13 0	1 7	6	3 82	<0 001

Table 7 Mean S-zin conc ntrations i the 14th week of gestation correlated to duration of gestation defined as week of delivery Stud t s t-test was used to compare 40th week with 42nd-44th and 35th-38th week

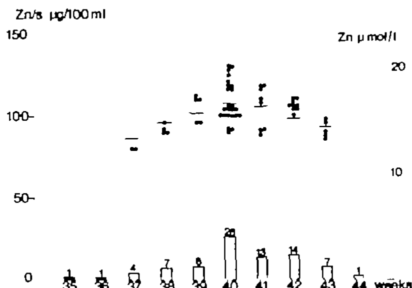


Fig 3 Distribution curve sho ing week of delivery orrelated to th serum zinc concentr tion (79 d ta) du ing a ly pregnancy The mean r indic ted Columns repre t the total um- be of d l ve ies (82 women)

Women del vered in the 40th week showed the highest mean serum zi concentratio s i e rly pregnancy Wome delivered o lier or 1 te showed lower mean serum zinc concentr tions in orly pregnancy Wome delivered in the 42nd we k or later howed significantly lower serum zin conce tr tions d ring early pregnancy tha tho delivered in the 40th week ($p < 0\ 005$) Wome delivered in the 38th we k or ea lier also howed significantly lowe conc tratio ($p < 0\ 005$) See T ble 7

Spontaneous abortion occ red in two ca s a few weeks ft the first amination Both patients showed a seru inc concentration of 16 5 µmol/l in the 13th week of ge t tion - the same figure as the mea i the ontrol group of non-pregnant women of f rtil age The serum copper conce trations in th se 2 wome few we ks before abo tio were lower (24 5 and 24 8 µmol/l) than in othe patie ts duri g the same week The serum vitami B-12 and f late co ce trations were normal

S ven women gave birth to immature infa ts and their data are li ted in Table 8 The wome showi g the lowe t s ru zinc con entration 10 4 µmol/l in the 12th we k of gest tion gave birth to an immature infa t (2 160 g) i the 36th week S T bl 8

Case o	1	2,	3	4	5	6	7
M ternal age years	21	17	22	20	25	24	20
Week of inve tigatio	13	13	15	15	12	12	13
S-Zi µmol/l	12 2	17 7	14 7	12.5	10 4	13 8	15 3
B-haemogl bi g/l	127	139	117	120	127	130	119
S-kobolamine pmol/l	206	184	224	191	320	390	199
S-fol te nmol/l	23	25	17	40	32	19	25
Bone ma row iron	I II	I II	II	I	trace	trac	trace
Week of delivery	37	40	35	38	36	37	38
I f t birth weight kg	2 00 2 58	2.49	1 97	2.38	2 16	2.16	2 38

Table 8 R lt of inve tigations i rly pregnancy in wome who gave birth to immat re i fants

The woman with the twin pregnancy showed low serum zinc in the 13th week (12.2 μmol/l) She gave birth to heterozygote girls in the 38th week (2 580 g and 2 000 g) The smaller twin was 44 cm long and her head circumference 31 5 cm She showed signs of cardiac malformation with a loud systolic murmur She developed cardiac failure with attack of cyano is Operation revealed a ventricular s ptum defect pred ctal coarctation of the a rta and symmet ical cardiac muscle hypert ophy and the infant died The other twin was perf ctly well The mother showed normal ha moglobin serum vitamin B-12 folate and bone marrow haemo id rin oncentratio s and normal bone marrow morphology in the 13th week of ge tat on She had rec ved only iron and vitamin supplements d ring pregnancy There was no history of infection du ing pregna cy and she did not dri k

Another woman uffered from d betes and was under treatment with insulin All laboratory investigations were ormal and she gave birth to a normal infant by ormal del very

D cu ion

It is known that the s rum zin falls during pregnancy The increase in plasma volume wh h reaches its maximum in the 25th week may partly explain this phenomenon (Lange 1973)

Certain d ta my co s con titute evidence agai st a major increase in pla ma volume In all but one the haemoglobin concentratio exceed d 110 g/l the theoretical limit for anaemia of pregnancy (WHO 1972) In all of them the blood pressure was normal and none showed oedema or prot inuria The rum protei s were not stimated however but all but 2 women howed normal vitamin B-12 nd folate concentrations which is some evid e th t the serum p otein co centration were not reduc d

None of the ome gave a history of rece t inf ction or showed igns of inf ction at the time of i tigation I fection causes econdary hypozincaem (Powanda 1973 B isel 1974)

The rum zi changes re procally with ch ge in glucocort coid levels (Henkin 1969 Dorn 1970 Flyn 1971) a d growth hormone con-

centrations (He kin 1974) During pregnancy there is a gradual i creas in plasma corticosteroid conce trations hich ttai level 2-3 times thos in nonpr gnant women This ncrease i most m rked during the third trimeste (Fri dma 1966) It corr ponds to raised concentration of the specifi tra sport prot in tra scortin which i turn is s condary to i cre sing oestrogen cti ity (DeMoo 1966)

I any one of these facto s sol ly responsible for the gradual slow fall i the seru zi c? It see s highly probabl that the xplana tion li s i a combi tio of them all si ce they may well all i t t the same time

Experimental zinc defici cy i l bor tory animals i associat d with increased incidenc f abortion abnormal parturition with incoordinate ute ine action and bl edi g (Apga 1968) i cre sed incide ce of congenital malformatio s and developmental di turbance (H rley 1966)

The two ubgro ps of pregnant wome G o p A and B may be regarded obstetrically uniform o that compariso s may be mad between them

I respective of how the se ies is l ssified - by ob tetri diagnosis o revised diagnosis i c ord c ith the defi ition of prolonged l bour (Willso 1971) or by d ration or labour alone the serum i wa significa tly lower du ing ly pregnancy both among women with bnormal labou and amo g wome in hom labour exc eded 20 ho s G oup B includ s also 4 wome with massive tonic bleeding d i g l bo r To judge from reports of animal e perime t it s em reason bl to i terpret the findi gs of low serum zinc d ing early pregna cy i mothers showi g bnormal l bou and/o givi g birth t immature i f t s an pressio of inc d fici cy

Wome delivered in the 38th week o e li or in the 42nd week o l t r howed significantly lower serum zi duri g ly pregnancy compared with wome d livered in the 40th we k Onc agai the e finding tally with re lts of pe ime ts on animal showing bnor mal period f gestation (Apgar 1968)

In two women parturition was complicated by ruptured cervix and lacerated perineum even though the infants birth weights and pres ntations were normal In both women the serum zinc had bee low duri g early pregna cy This phenomenon may be dependent on zinc metabolism as zinc is apparently of importance in connexion with collagen deposition (Westmoreland 1971 Fernand z-Madrid 1971) and the tensile strength of tissues (Sandstead 1970) The same fi dings of low serum zinc in women with perineal tearing were reproduced in another 6 cases (II)

Seven women gave birth to low-weight infants and 6 of them w re delivered before the expected date These wome had shown significantly lower serum zinc duri g early pregnancy than the normal Group A women Among the very few pregna cies that have been reported in wome s ffering from acrodermatitis teropathica two have resulted in low weight inf ts nd on of these wa malformed (Verburg 1974 Hambidge 1975)

Mother of low weight infants showed low zinc conce trations in the amn otic fluid (Favier 1972)

M lformations in the off pring of zinc deficient female nimals have bee r ported All type of anomaly have been found including malformations of the c tr l n rvous system cardiac defects and mul tipl skeletal malformations (Blomberg 1960 Hurl y 1966 Swenerton 1969 Warkany 1973)

On of the 83 inf t in my s ri s showed a conge it l c rdiac malformation w th a ventricular septum d fect and coarctation of the aorta H r mothe had hown the lowest serum inc recorded in the 13th week of ge tation but all other laboratory findings wer normal She gave h story of i fection or suspe t medication and she did not dri k (An association betwe maternal chronic alcoholism and congenital malformations in the infant has be noted Jones 1973) The twin-sist r of the affected infa t was no mal but of low weight It i possibl that low serum i c values together with other factors s ch as differ t si d place ta with diff rent blood flo s may have co tr but d to the malformation

A conne io betwee at rnal zinc deficie cy and congenital malforma tions h be n postulat d (Halsted 1973 S ver 1973 B ch 1975 Hambidge 1975) The infant with the cardia d fect provides vid c i suppo t of the s spicio th t i c d ficie cy ay t t ratoge ically in man

The factors governi g the d r tion of pr gn cy re ot fully under tood and it i not known why delivery tak s plac ft r 280 days The findi gs of low erum zinc value i e rly pregnancy in wome i hom parturition took pl ce too arly or too l te s ggest that processes directly o ndirectly influe ci g the serum i r i ome way a so iated with these governi g factors

The significantly highe s rum opper conc tration f nd d i g arly pregnancy i Group B wome with compli tion t d livery compared with the ormal G o p A may be i terpret d a bei g condary to raised oestroge prod ctio I cr ase of oe t oge s is soci t d with incre ses in the s rum coeruloplo in (Mandorf 1971) The high copper concentration may l o be s co dary to an increase in int ke of copper salts i food o wat r

E perime t l a imals show sig of zin deficie cy f the amo t of coppe i the food i relatively higher tha the amo nt of in Zi suppl me t cou t ract thi ff ct (S ttl 1966)

There i a intera tio betwee inc and copper p obably competi tion ove lfhydryl-bi ding sit s o metallo-thionein (Eva s 1970 Whanger 1971) Raised coppe conce tration ight therefor accentuate any zinc defi i y

It h s ot been est bli hed whether the low rum inc ncentration demonstrated in thi se i s of pati ts do in f ct refl ct st te of in defici cy but the si il iti t the ffect of perime tal inc d fici cy i animals re st iki g The high inciden of complication ff ting mothers a d i fant wh low serum i concen tration had bee recorded in ly pregnan y o ther rel vant d fici i s bei g demonstrabl gge t that the finding is of gre t importanc

Summary

Serum zinc and serum copper conce trations during early pregnancy in 84 consecutive primigravidae were correlat d to other haematological factors a d were also correlat d to complications of labour and/or complications affecting the infant

In women with complications such as abnormal labour or atonic bleeding serum zinc concentrations were significantly r d c d ($p < 0\ 001$) during early pr gnancy Wom n who gave birth to immature info ts also howed significantly lower rum zinc in early pregnancy ($p < 0\ 01$) Women d liver d in the 37th week or earlier or i the 43 d we k or later show d significantly lower s rum zinc during early preg a cy ($p < 0\ 005$) compared to women deliv red in the 40th week

O e infant showed a congenital heart def ct (ventricular sept m defect a d pred ctal coarct tion of aorta) Her morther showed the lowest serum zin concentration recorded in the 13th we k but no other abnormal findings

Co pared to women with abnormal labours and/o immatur inf ts mothe s with normal d liveries and or al inf nts showed significant ly higher s rum inc valu s ($p < 0\ 001$) and ignificantly lowe serum copper oncent ations ($p < 0\ 025$) d ring early pregnancy

A ot bly high in idence of co plications affecting mothers a d infant has be n record d among wome with low serum zinc Simil rities to ffect of e perime tal zinc deficiency in nimals are t iki g

If a low serum inc flects a st te of deficiency nd this s ems to be the ase inc d fici n y is p obably common

VARIATIONS IN MATERNAL SERUM ZINC DURING PREGNANCY AND CORRELATION TO CONGENITAL MALFORMATIONS DYSMATURITY AND ABNORMAL PAR TURITION

By

St Jame o

It is known that the s rum zinc d r s during pregnan y (I) The fact that this phenomeno r flect altered zi c metab li m i confirmed by the observatio that the zi c cont t of hai i lowe i the 36th we k of ge tation than i ea ly pregn ncy (Hambidge 1974)

A low erum zin eems to imply i ks to mother nd child (I) a d i sociated with complicatio s d i g l bou and with anom li s of maturity in the infant One woman with low seru zinc in my seri s gave birth to a gi l with a conge ital heart alformation

This p o pe tive study wa de igned to investigat spected con ion between rum i c a d maternal or foetal complication and to registe the va iations i serum zi d ri g pr gna cy

Mat l and methods

Gravid attending th Antenat l U it Region l Hospit l Örebro were i ve tigat d outi ly throughout p gnan y Blood sampl were obtai d from cubital vei at 2 p m more than 2 hou ft the late t meal ing t i l ss dispo bl ne dl s and cid- i ed gl ss t be with pl ti p Con e t wa obtained in 11 c ses Speci l ffort wer mad t fi d wome with a pa t hist ry f complication of pregnancy and pe i l-ri k cases (g twi pregnan- i di betic mother)

Altogethe 245 gravidae were amined (mean ge 25 4 ye rs ra ge 16 41 SD 4 3) Spont neous bortion occ rred i 11 case and the were luded The remai ing 234 women upplied 493 mpl s of serum t diff re t week of ge tation Ninety si pati ts were re

presented by only one sample

Zi c and copper estimatio s were carried out by atomic absorption spectrophotometry at the Department of Environme tal Health Örebro as described elsewhere (I)

The 24-hour excretion of oestriol in urine was measured in 21 cases and analysed at the Departme t of Clinical Chemistry Örebro (Frandsen 1963) The serum chorionic somatomammotrophin (HCS) was analysed by radioimmunoassay in 19 cases at the Serological Laboratory Örebro

Data concerni g blood loss at delivery duration of labour and birth weight were obtained from case records along with clinical obstetric and paediatric obs rvations

Statistical analys s were done by computer using mean value a alysis regression nalysis and Stud t s t-test

All laboratory data ar rec lculated to SI nits

Results

The s rum inc co centration falls gr dually d ring the first and seco d trimesters but becomes stabiliz d from the 25th we k ntil delivery See Fig 1

A ormal ref rence curve describing variatio s i serum zi c wa construct d usi g the following crit r a: maternal haemoglobi x eeding 110 g/l t each sa pling; maternal blood pressure ever exceeding 150/90; absence of proteinuri th oughout; delivery d ring 39th 41 t week ; d ration of labou less than 20 hour ; bleeding at part rition l s tha 300 ml; 3 or more serum zinc stimations during pr gna cy The e cr teria were f lfill d in 18 cases with altogether 62 inc stimatio The graph shows a low significant d crease as pregna cy proce d (r -0 52 p < 0 005; Fig 2)



Fig 1 The di tribution of 493 serum zi c co centration f om 234 gravidae ac ordi g to week f gestation Readi g from 8 wome who gave birth to malf rmed i f nt a marked by asterisks

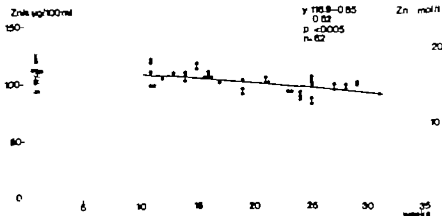


Fig 2 The di tribution of 62 s rum i c concent tion from 18 normal pregna t wome c di g to c it i i t xt Figures i the equation of the regre ion li are - pr sed as µg/100 ml Ope circl normal gr up (I)

The individual values showed very little variation; in other words the individual zinc level seems stable No low values were recorded

Twenty two gravidae gave birth to 28 immature infants Labour was in duced before the expected date in three cases with normal serum zinc owing to uterus bicornis placenta praevia and hepatosis gravidarum

Four infants were classed as small for date

Eight infants showed congenital malformations of different types and severity Five mothers of these 8 showed the lowest serum zinc concentrations registered in the respective week of gestation (Tabl 1 Fig 1)

S-zi c µmol/l	n	mean	SD	SEM
Total material (493 obs)	234	14 6	2 0	0 1
normal pregn cy as defined (62 obs)	18	15 3	1 5	0 2
immature infants	22	13 9	2 1	0 4
small for-dat	4	14 3	3 0	1 5
malformat ons	8	12 3	1 7	0 6
dysmat infants	13	13 0	2 1	0 6
prolo ged pregnan y	6	11 5	1 0	0 4
abnormal deliverie	50	13 2	2 0	0 3
G oup I	145	14 5	2 0	0 1
Group II	89	13 3	2 0	0 1

Tabl 1 Di trib ti of mean serum zinc in diff rent groups as defined i t xt umber f women/group Exc pt when oth r i t ted each pati t is repre nted by th lowest zinc alue that as recorded Six of 50 women with abnormal deliver s d veloped uptura rvici o ruptura perin i (mean S ı c 13 1 µmol/l SD 0 8)

The diagnosis of dysmaturity was ad i 13 infants of 13 mothers; the maternal zinc conce tr tions are li t d in Tabl 1

Fourteen others who gave birth to abnormal infants d livered lso bnormally

Altogethe 50 abnormal deliveri occurred (see Table 2 for detail) and in 6 wome l bour was induc d owing to a prolonged pregna cy The 56 are grouped togethe as wome with abnormal d live s

Part protract s (5) + CS (5) + VE (7)	17
Haemorrhagi to ic i tra pa tum	4
Ablatio plac ntae	4
R tentio placentae	3
P c sphyxi f t imine + VE (4) + CS (2)	6
P po itio f tus abnormis	3
P complicat s (t rus bicornis pelvis gu ta place ta praevia) + CS	3
P c ins fficienti placentae (diabetes matri) + CS	4
P c l c ratione c icis vaginae pe l l	6
	50

T bl 2 Complication i 50 wome ith bn rmal deliveri s
CS Cae a ean se tion VE = vacuu xtra tio

Of 234 gravidae 145 had normal deliveries at the expected time and the infants were normal; these 145 women are called Group I

Eighty-nine women (22 + 4 + 8 + 13 + 56 - 14) had abnormal deliveries and/or abnormally developed infants; these form Group II

Each individual patient is represented by the lowest serum zinc concentration recorded during pregnancy

Compar d to the normal Group I women 56 patients with abnormal d liveri s showed significantly lower s rum zinc during pr gnancy ($p < 0\ 001$) Table 3

S-zinc µmol/l	n	mean	SD	t	p
Group I	145	14 5	2 0		
Group II	89	13 3	2 1	4 14	< 0 001
abnormal deliveri s	50	13 2	2 0	3 82	< 0 001
dy motor infants	13	13 0	2 1	2 53	< 0 02
malformation	8	12 3	1 7	3 06	< 0 005
immatur infant	22	13 9	2 1	1 27	< 0 3 N S

Table 3 Diff r ces between mea s analysed by to Student s t-t st When t sting Gro p I again t other groups the probability of diff ence wa c nside ed t be significant when p was l than 0 05 umber of wome /group

The 22 wome with immature i f ts showed lower serun inc than Gr p I but the differe ce wa not signifi ant (p < 0 3)

The 13 mothers of dysmature infants howed serum zi c co ce tration significantly lower than Group I (p < 0 02)

Mothers of malformed info t also showed ignif cantly lowe s rum inc than Group I (p < 0 005)

Group II had significantly lower erum zi d ing pregnancy than Group I (p < 0 001) The groups are comparabl There i no signi ficant diff rence betwee th m with regard to the time when the lowest inc co centration was recorded mean value con ring th we k whe the low st inc conce tration wa recorded did t diff r significa tly (Gro p I 20 3 Group II 21 9 p < 0 2) This very small differe ce i time c ot e pl in the diff re t zi co ce trations

The zin conce tration in Gro p I are lower than those in the ormal primigravidae (I) The differenc c rresponds to the mean fall in serum zin seen from the 14th to the 21 t weeks (Fig 3)

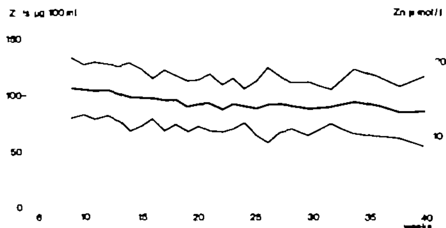


Fig 3 The dist ib ti of means and 2 stand rd d viations from 493 s rum zi c timation (see als Fig 1)

In 21 patients simultaneous estimations of 24-hour urinary oestriol excretion and serum zinc were done There is no correlation between these values (Fig 4)

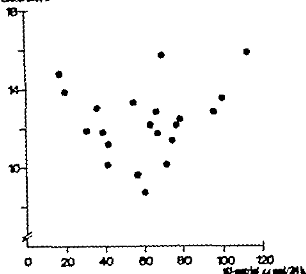


Fig 4
The distribution of *urinary oestriol excretion*/24 h correlated to serum zinc

In one case a diabetic woman ther was a sudden fall in oestriol excretion but no change in either serum zinc or serum copper In 19 patients s rum zinc and serum HCS values were recorded simultaneously There was no correlation between these values The very high figures for HCS were not associated with low serum zinc (Fig 5)

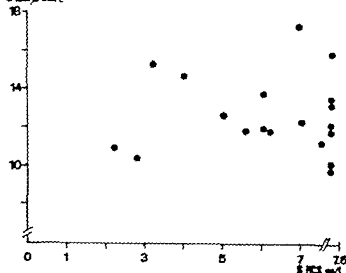


Fig 5
The distribution of serum HCS correlated to the concomitant s rum zinc

Eight infants showed congenital malformations

One boy had a hydrocoel testis His m ther had i the 19th week serum zinc lightly above the me (Fig 1)

One boy had praelu atio co ae In the 13rh and 18th weeks his mother showed serum zinc conce trations j st over the means for thes periods.

One boy born in the 39th we k had und scended testes His mother showed serum zi c co centrations bout one stand rd deviatio below the mean i th 16th and 28th week Th remaining 5 infants are re ported in more d tail

Case 1

A girl birth weight 3 400 g dysmature born afte induction of l bour i the 43rd we k At birth sh had a loud ystolic murmu S b-sequent investigations have reveal d ve tricul r septum defect left devi t d el ctrical axis and p olonged PQ-time Further investiga-tions ar pla ned I the 13th we k he mother showed the following: S-zinc 12.5 µmol/l S-copper 31 7 µmol/l B-haemoglobi 128 g/l; in the 17th week the followi g were ot d S inc 11 3 µmol/l S-coppe 39 2 µmol/l Her seru zinc was lowest in th 13th we k nd next lo-west i the 17th week Sh gave history of inf ction d i g preg-na cy re ived only iro and vitamin supplement and did not dri k The th was a II-gravid ged 25 years with a hi t ry of one spon taneous abo tion

Case 2

A boy birth weight 2 000 g l gth 41 cm immat re born i the 33rd week Cae arean section was done owing to falling oe triol ex cretion The i fant died few hou l te in re piratory di tres ynd ome He showed multipl skel tal malformations double l ft hallux s veral he ivert brae in the lower thora ic and lumba re-gions seve al ight id d co tal a omalies and doubl ight kidney

Hi the wa 22 yea -old I-gravida She had s ff red f om insulin-treat d di bet s si ce the ge f 8 and wa well controll d on a two-dose regime She showed no ketosis or protei i The s rum

creatinine was normal (90 µmol/l) and the blood pressure normal There was slight retinopathy In the 21st week the following were recorded: S-zinc 10 8 µmol/l S-copper 26 2 µmol/l B-haemoglobin 110 g/l S-protein 72 g/l S-albumin 39 g/l S-alkaline phosphatases 1 3 µkat/l (normal range 2 0 - 5 0 µkat/l) S-HCS 2.2 ng/l (normal 0 9 - 2.5 ng/l) In the 23rd we k the findings were: S-zinc 10 6 µmol/l S-copper 25 4 µmol/l S-HCS 2 7 ng/l (normal range 1 3 - 3 4 ng/l) The serum zinc concentrations were lowest and next-lowest in these weeks

Apart from insulin therapy and iron and vitamin supplements she r - ceived no other medication suffer d from no infections and did not drink

Cas 3

A boy birth weight 3 630 g born by normal delivery in the 40th week H showed hypospadia His mother a 30-year-old II-gravida gave no history of infection during pregnancy In the 12th we k the following were record d: S zinc 11 6 µmol/l S-copper 39 9 µmol/l B-haemoglobin 128 g/l The blood pressure was normal and there was no protein ria She received no medication other than iron and vitamin suppleme ts There was a suspi ion of alcoholism The serum zinc was lowest in the 12th week of pregnancy

Case 4

A boy birth weight 3 400 g dysmature born in the 43rd week Par turition was p olonged and complicated by haematoma vulva The boy had und sc d d testes His mother a 25-year-old I-gravida showed in the 16th week the following: S-zinc 12 8 µmol/l S-copper 34 8 µmol/l (the third lowest zinc conc tration); in the 22nd week the figur s we e S z 10 7 µmol/l S-copper 37 7 µmol/l (the lowest zinc concentration r co ded) B-haemoglobin 120 g/l The blood pres sure a no mal d ring the first half of pr gnancy During the third trimester the blood p e s r was slightly raised and there was slight protein ri but t eatme t was given She had no infections did not drink d r eived only iron and vitamin supplements

Case 5

A gi l birth weight 3 650 g born by ormal delivery i the 40th week She had preluxatio oxae Her other a 33-year-old I-gra ida showed in the 14th week the followi g S-zin 11 9 µmol/l S-coppe 32 3 µmol/l (the lowest zi conce tration) I the 23rd week the following were found: S-zin 12.2 µmol/l S-coppe 36 4 µmol/l (the third lowest serum zin) B-haemoglobi 105 g/l She received o medi ation other than iron and vitamin s ppl ment and the haemoglobin r se to 137 g/l The blood pressure wa ormal nd ther was o protei uria She gave no history of i f ctio and did t d i k

El ve gravida in whom bortion lat r occurred were xcluded from the seri s of 245 wome Spontaneous bortio als occured in 2 out of 84 primigravidae (I) The 13 wome are g ouped together as wome with abortions and showed compared to deliver d p imigravidae (I) ignifica tly lower s rum opper i early pregnancy (p < 0 001 T bl 4)

	mean	SD	SEM		t	p
S zinc (all bortion)	16 2	1 8	0 5	13		
S-copper (all abortions)	23 8	5 1	1 3	13		
S zi c (sponton ou b)	17 0	1 0		10		
					5 22	< 0 001
S zi c (mi sed b)	13 5	1 1		3		
S-copper (ponton ou ab)	22 7	3 2		10		
					1 47	< 0 2 N S
S-copper (mi ed b)	27 4	8 9		3		
S-coppe (primigra idae)	36 2	7 6		77		
					5 63	< 0 001
S-copper (ll bortion)	23 8	5 1		13		

T bl 4 Mean S i and S-copper in µmol/l Groups are d fined in t t Compari on was mad with 77 delivered p imigravid e (I) and betwee g oups of wome with spo taneou bortion and missed abortion

Three women in whom missed abortion later occurred showed significantly lower serum zinc values ($p < 0.001$) than 10 with spontaneous abortion Women with spontaneous abortion showed serum zinc concentrations in the same range as fertile non-pregnant women (I) In 6 cases there was clearly abnormal serum copper or serum zinc 4 we ks or more before abortion (Table 4)

Discussion

The serum zinc falls slowly as pregnancy progresses but the mean value becomes levelled out from the 25th we k Some women show a low serum zinc in early pregnancy The serum zinc concentration appar ntly varies little in the indi idual woman with uncomplicated pregnancy

The cause of the gradual fall in serum zinc must be sought among several possible mechanisms Pla ma volume expansion which normally takes place during pregnancy must be one explanation: the shape of the graph for serum zinc with levelling from the 25th week is evidence in favour of this and the ph nomenon has also been r produced in plasma-volume investigations (Lund 1967)

Oestrogens have be n shown to reduce the serum zinc (Halsted 1968 McBean 1971) If these were one of the most important zinc-lowering fa tor the readings would continue to fall during th third trime ter wh n oest agen production reaches its maximum The same would be true of HCS and progesterone No correlation was found between serum zinc and oestriol excr tion in urine or between serum zinc and HCS In one case a sudden f ll in oestriol excr tion fail d to evok a change in s rum zinc or copper in a diabetic woman with placental insuffi i ncy

Thes hormones would appear to be of minor importance with regard to low s rum zinc conc t ations

No curr nt inf tions were r gistered in any patient at the time of investigation The serum zin falls as a r sponse to infection (Burch 1975) Such f tors nnot have influenced our data

Hypertension and pr tein ia were regi tered in only a few ca s and cannot have influe ced the fi ding

As some women have low s rum zinc valu early in pregna cy before the rapid increase in plasma volume a d hormone production takes plac other factors must be considered If changes in serum p otein can be excluded zinc defici cy would be the most probabl e pl na tion

A g oup of 18 women with normal pregna cy and ormal delivery with normal infants showed strikingly st bl serum zi c conce trations ith light slow decr

Women with ormal d live i s and ormal infants (Group I) howed significa tly highe seru i du i g pregnancy tha the Group II women with omplications ($p < 0.001$) These res lt tally with a li findings (I)

Women with immat re infants showed in ignific tly lowe serum zi value than Group I Three of them howed normal serum zinc values and the ca se of immaturity was obst t i

Women whose infants were dysmat re showed significantly lower serum zi c values than Group I ($p < 0.02$) Thes re lts re in c rda c with earlie findings (I)

Six wome with prolonged pregnancy showed low serum inc which t lli with ea li r re lt (I) (Gro prolongata by di gno is)

These findings t ongly gge t that lo s rum inc refl ts factors of importanc with regard to duration f pregnancy fetal d velopment d effi i cy of labour

Among 234 births 8 i fant howed conge it l nomalies of differe t types nd severity Their mothers howed significantly lowe s rum inc tha Group I ($p < 0.005$) Routine i ve tigations ca ied out duri g pregnancy provided no othe lue to the malformation (i travenou gl cos tol rance te ts were ot perf rmed) On moth r whose

infant showed multiple skeletal malformations had had diabetes since the age of 8 years The incidenc of malformations is raised among infants of diabetic mothers (Pedersen 1964) Several studies suggest an interrelationship between insulin and zinc Impaired glucose tolerance has be n observed in zinc d ficient rats (Hendricks 1972) The true cause of the increased incidence of malformations among infants of diabetic mothers is not known however

Low s rum zinc concentrations have be n reported in patients with hepatic cirrhosis (Vallee 1959) Low zinc values have also been recorded in non-cirrhotic alcoholic patients the concentrations returning to normal during periods of abstinence (Sullivan 1965) A variety of malformations have been reported among children of severe ly alcoholic mothers (Jones 1973) including cardiac anomalies and congenital dislocation of the hip There is no information about the zinc status in these women

Very few pregnanci s (7 or 8) have occurred among women with acrodermatitis enteropathica and two severely malformed infants one with anencephaly and one achondroplastic dwarf have been reported (Hambidge 1975) This condition is totally reversible when zinc therapy is given (Moynahan 1974) Low alkaline phosphatase activity has been described in one case the enzyme activity rising rapidly when zinc therapy was instituted (Neldner 1975) The finding of low alkaline phosphatase a ti ity concomitantly with low serum zinc in the diabetic mother whose infant showed multipl skel tal malformations (cas 2) might possibly fit in with these observations

A connexion between human maternal zinc d ficiency and congenital malformations has been postulated by s veral writers (Halsted 1973 S ve 1973 Burch 1975 Hambidge 1975)

Experimental zinc d fici n y in gestating animals is associated with a high incidence of fetal malformations of different types aff cting for example the entral n rvous and skelet l systems and the heart (Hurl y 1974) A high rate of resorption of implantation sites has also been recorded

The findi g of 5 info ts w th diff r nt types of co ge ital alfo mation and in ea lier series one i fant with ventricul r s ptum defect nd coarctation of the aort (I) whose othe s showed the lowest serum zinc oncentrations record d nd the fi di g of low serum zinc in 3 women who b quently d veloped m sed bortion, con situte convinci g evide ce that zinc deficiency occurs during huma pregna cy and may act t ratoge ically

Low serum copper have bee report d in gravidae who d lop spont neous abortions (Heijkenskjöld 1962) Low opper co ce tr tions may indicate damage to placental t ss s (F iedma 1958)

Why should wome with abnormal labour show lower s rum zi tha women with normal deliveri s? A certain inc conce tratio to be nec ss ry for and to pot ntiate twitch r sponses i sk l t l muscl (Isaacson 1963 Edman 1966) Zinc can als pote ti te ont actil re pons s in rat ut ru (Daniel 1971) Impa red mu c la pe forma may be ssumed to acce t at y purely ob t t ic complication of delivery No matter what th planation i the fi di g of low ru zin du ing early pregnan y in wome ho later had bnormal d liveri s have been reproduced i two s ies of gravidae Thes fi dings must be ssociated with f tors sse tial f r the performa ce of l bour

Zinc balance wa studied i 4 teenagers d ring the la t trimester of pregnancy (Schroe 1974) A zinc ret tio of 3 6 mg/day was observed together with it ogen retention of 2 8 g/d y This mean that fo the normal weight gain of pregna y of 12 5 kg at l ast 375 g of zi c would have to be retained To this requireme t of 375 mg mu t be added a extra ppl me t to compensat fo daily lo se via hair kin nails sweat uri e and faeces

The lowe concent tion of zi c i hair d ring late pregna cy (Hambidge 1974) may be a ff t of negative zinc balance re lti g in zin d fi i cy

The addition l requireme t f at lea t 375 g of inc duri g pregnancy is related to the t tal body i (2 - 2.3 g) in the same f shion the tra iron req irement f pr gnan y of 600 - 1 000 mg

ZINC DEFICIENCY IN MALABSORPTION STATES: A CAUSE OF INFERTILITY?

By

Sten Jameson

A human adult contains about 2 gram of zinc (Vallee 1959) The serum zinc is about 15 µmol/l (Pekarek 1972 Hahn 1972 Wester 1975) The absorption of zinc seems to take place in the proximal part of the small intestine but the exact mechanism in man is not clear (Halsted 1974 Burch 1975)

Zinc is excreted mainly via the gastro-intestinal tract in the fae ces (Cotzias 1962) but is also lost via sweat urine semen hair nails and skin (Schroer 1974) and via mothers milk (Berfenstam 1952) The dietary zinc seems to parallel the energy content and a mean daily intake of 8-9 mg of zinc has been recorded in Sweden (Abdulla 1974)

Zinc deficiency in experime tal animals causes changes in hair skin and cla s (Barney 1968) Fertility is also impaired and the number of abortions incr ases The incidence of malformations in the off-spring increases and parturition does not occur at the right time and is characterized by abnormal labour and heavy bleeding (Blomberg 1960 Hurley 1966 Apgar 1968) Testicular tubules in rats show de-generative changes i zinc deficiency and administration of zinc quickly results in reversal (Diamond 1971)

Zinc d fici ncy in man has been found to be responsible for the in-herit d ondition acrodermatitis enteropathica which is cured by zinc therapy (Moynahan 1974) Among the 7 pregnancies known in pa-ti ts with this condition 2 infants showed sever congenital mal formations (Neldner 1974 Vedder 1956)

Low serum inc ha bee report d in a few pat nts with malabso pt on (MacMahon 1968 Caggiano 1969 Walker 1973) i cl ding some with glutensen itive e terepathy and d rmatitis herpet formis One cas ha been desc ibed of regio al enteropathy retarded g owth and hypogo- odism with zinc d fici ncy hich re ponded well to zinc s pplemen tation (S dstead 1970)

Low co ce trations of zinc were found in th hai of 23 pati nts with coeli diseas (Amado 1975) Childre with poo gro th anore i and hypogeu ia show low hair zin (Hambidge 1972)

Three women with coeliac dise se and i f rtility of long duration conce ved and gave birth to normal fonts by normal delivery aft institutio of gluten-fre di t and normali ation of bowel fun tion (M rri 1970)

Two me with coeliac disea i f rtility and dys-spermatoge si have also be n reported Normal permatogene is was tabli hed after the i tit tion of gl t fre d t d on of the men sub eque tly became a f the (Merianos 1975)

A b y with coeliac d delayed puberty and retard d growth d veloped adult growth nd second ry sex-chara ters du ing and ogen therapy but spermatogene i was tabli hed only aft the pati nt had bee placed on a di t conta ing glut free flou (Fos 1962) No t ts of i met boli m were done i any of the cas In orde to i ve tigate whether i c d fi ie cy f rm part f the mal b orp- tion pi t re the followi g study wa arried out

Mate i l and method

S ven women and 6 me were ref rred to the Departme t of Medicine o cli i al picion of mal bsorption They were inve tigated as i pati t Blood sampl s were t ke f om fa ting pati nts i the mor ing

The haemogl bi wa stimated by the cyan-methaemogl binmethod The serum vitami B 12 (S-kobolamine) was ayed by the radio-immune t chniqu S rum folate (S folate) an lysis was done microbiologi-

cally Th zinc and copper concentrations in serum and urine were assessed by atomic absorption spectrophotometry at the Department of Clinical Chemistry Regional Hospital Örebro

Faecal fat was analys d from samples of 3 days stools after the pa tient had been receiving a standardized diet containing 70 g of fat/ day An excretion of mor than 23 mmol/24 h (7 g fat) was considered as st atorrhoea The D xylose test was regard d as abnormal when less than 20 % of the dose was cleared into the urine within 5 hours
The serum proteins were assessed by an electro-immunochemical techniqu (Ganrot 1972)

The HCL production was estimated after pentagastrine stimulation
Biopsy of the small intestine was done with the aid of Carey or Cros by capsules

Bone marrow was aspirated from corpus sterni The bone marrow haemosiderin was estimated on a semiquantitative scale (I)

Results

All 13 patients showed lo or very low serum zinc concentrations On*ly 4 showed mark dly decreased serum albumin None showed increas d* haptoglobin concentrations Only one showed a raised orosomucoid level indi ating inflammatory reaction

All data and the r lts of the investigations are listed in Tabl s 1 and 2

The uri ary exc etion of zinc was low in all 8 pati nts investigated Eight of 12 patients showed pathologically low serum folate concentrations Three of 12 pati nts showed subnormal or pathologically low serum itamin B 12

In 8 of 12 p ti nt the bone marrow haemosiderin was totally lacking or pr sent in only trace quantities

Ten of the 13 pati nts showed abnormal D-xylose tests Nine of 12 had steatorrhoea Eight of 9 had a hylia Eight of 10 howed total or

Patient no	Sex	Age	D-xylose test	Faecal fat mmol/24 h	HCL production	Intestinal villi	Effect of gluten free diet	Diagnosis
1	F	39	abnormal	48	achylia	-	good	C D
2	F	38	abnormal	44	normal	total atrophy	good	C D
3	F	49	bnormal	128	achylia	total atrophy	good	C D + D H
4	F	58	abnormal	27	achylia	subtotal atr phy	good	C D
5	F	72	abnormal	35	achylia		-	C D + D H
6	F	68	abnor al	31	chyli	total atrophy	good	C D
7	F	46	normal			total atrophy	good	C D
8	M	15	abnormal	2	-	-	good	? C D + D H
9	M	25	normal	19		normal	poor	P-L E
10	M	56	abnormal	41	achyli	subtotal atrophy	good	C D
11	M	67	normal	29	achylia	ormal		B II sequelae
12	M	68	abnormal	45	achylia	total atrophy	good	C D + D H
13	M	59	abnormal	17	-	subtotal atrophy	good	C D

Table 1 Age and sex distribution of 13 patients Results of malabsorption tests and diagnos s
C D coeliac disease D H = dermatitis herpetiformi B-II Billroth-II operation
P-L E Prot i losing teropathy

Patient no	S-zinc µmol/l	U zinc µmol/24 h	S-copper µmol/l	S albumin g/l	S-orosomucoid g/l	S haptoglobin g/l	S-kobol min pmol/l	S folate nmol/l	Bon marro haemo-siderin
1	7 6	13	20 4	43	0 8	1 5	94	3 5	0
2	6 0	-		32	-	-	146	2 2	0
3	7 4	10	11 0	41	0 8	0 9	130	10 0	0
4	9 1	3 1	18 9	38	0 8	1 2	280	15 0	II
5	12 0		11 2	39	0 8	0 6	140	2 4	0
6	6 9	2	-	35	0 8	0 8	220	2 6	trace
7	4 9	2 7	22 0	44	-		112	2 3	0
8	7 3	13 5	-	45	1 0	0 9	-		
9	7 3	1 5	11 0	25	2 8	1 3	510	5 2	III
10	7 1	-	-	31	0 8	1 2	250	2 5	t ace
11	10 6	-	11 4	40	0 7	0 9	146	29	0
12	10 6			43	-	-	73	40	I
13	12 8	6 2	17 3	42	0 8	0 8	130	5 7	II
Normal	13–20	21 119	13–26	40–52	0 5–1 4	0 3 1 6	100–750	7–34	II

Table 2 L boratory data of 13 patients and normal ranges

subtotal villous at ophy T n of the patie ts i proved after th institution of a glut n free diet one refused thi regime one man f iled to improve and in nother it was not recomme ded

All 7 wome and 3 me were give the diagno is of coeliac dis s ; one boy with dermatitis herpetiformis w s diagno d as s spected coeliac dis se

All 7 women complained of i f rtility of differe t d ation and re reported i detail below All gave hi tory of n rmal me strual cycles

Case 1

A 39 year-old woma who had suff red from periodic di rhoea since puberty She became pregnant at the ge of 25 and gave birth to an infant with bilateral congential di location of the hip after an b-normally long labour (25 hours) She wished for more hildre but did not conceive agai Gynaecological investigation t the age of 32 fail d to pro id n e planati of her infertility At the age of 39 she was found to have coeliac diseas and treatment with glu te fre di t vitamin B 12 folic acid and i on was instituted

Five month later the serum zin was still low (8 3 µmol/1) The gluten fre regime had been uns cc ssf l owing to pi fo rye c i p-bread Zin suppleme ts (45 g Z^{2+} twice daily i c s lphate S lve in ^{R}) were give Afte ne week of tre tment the rum zi had incre d to 9 3 µmol/d and the in ry e ti n of inc from 2 0 to 7 3 µmol/24 h Afte one week tre tment the patie t concei ved despite 14 yea s of inf rtility On ami tio afte two months ame or hoe the l boratory t t of pr gnancy was po itive and t ine g wth corresponded to the 9th week of pregnancy Aft 11 we ks spont neou abortion took pl ce The rum i c wa not stimated at that time

C s 2

A 38-ye -old woma who had on ived t the ge of 26 afte two ye rs of ma iage Aft bnormal labour (27 hours) she gave birth to a boy who showed igns of cardiac malformation He died at 4

months of age at operation Necropsy disclosed hypoplastic right chamber a small ventricular septum defect tricuspid atresia pulmonary stenosis hypoplastic pulmonary artery atrial septum defect bicuspid valve in the pulmonary artery and left chamber hypertrophy

The patient then tried to conceive again but failed Gynaecological xamination at the age of 30 provided no explanation At 38 years she became pregnant but aborted spontaneously after 2 months Co t-raceptive steroids were given for the next 2 months but the patient developed s vere diarrhoea Investigation disclosed coeliac disease with total villous atrophy Gluten-free diet produced rapid improve ment

The patient s mother gave a history of 3 pregnancies. The first resulted in a pr matur infant (birth weight 1 550 g) that di d During the second and third she suffered from severe anaemia and was given liver preparation and blood transfusions At the age of 57 she was found to have coeliac disea e and gluten fr e diet was institut d

Case 3

A 49 yea -old me opausal oman who had suffered from periods of diarrhoea and dermatitis herpetiformi ince the age of 25 Gynaecological a inat on t the age of 34 had failed to e plain her in f rtil ty The present investigations disclos d coeliac disease Si ce the institution of glut n-fre diet the patient has become totally fr from symptoms and signs At the start of the regimen suppl mentation w th zinc-sulphate (45 mg Zn^{2+} twice daily Solve-inc [R]) fo one ek p od ced an increase in serum zinc from 6 4 to 10 2 μmol/l and the i ary zinc increased from 1 5 to 5 8 μmol/24 h

Cas 4

A 58-year-old post-me opausal woman wh had suffered from periods of diarrhoe si ce the age of 35 She married at the age of 40 and desired childre but failed to conceive The present investigation disclos d coeliac d seas The patient has had no bowel symptoms since the i stitution of glut n-free diet

Case 5

A 72 year-old woman with a history of bro ch al asthma and periodi diarrhoe since puberty and dermatitis herpetiformi ce r ddle age She married at the age of 20 desired childre but failed to conceive Examination ow showed signs of coeliac d s ase Treatm t with iron vitamin B 12 and foli acid did not mitigate he symptoms and signs She is troubled by cheilitis glo sodynia and deep fis s res of the fingertip and heels in ddition to he dermatit s h - petiformis She has decli d a gl t n-free di t

Case 6

A 68-ye r-old woman with a history of d rmatitis h rpetiformis ince the age of 35 and dia rhoe fo th pa t 3 years She marri d at the age of 20 wanted children but d d not c nceive Wh he as 30 years old she was found to have ve e a aemia and wa treated with liver preparations The prese t inve tigation di los d coeli c dis as Gluten-free diet produc d prompt reli f of the diarrhoea and skin eruptions

Case 7

A 46-year-old woman complai g of head che and fatigue but not of bdominal pain o di hoea Investigation dis losed anemia with iron and folate def iency and total villous atrophy Coeliac di ea e was diagno ed She ma i d at the age of 20 became pregnant at the age of 29 and gave birth to a rmal child by ormal d l very She d sired m re children b t f il d to on ive A gl t n-free di t gave rapid improvement and the anaemia disappeared

The 6 men with mal bso ption were not inve tigated with regard to f rtility Fou of them w re ove 50 ye rs of age and gave short histo i s of bowel di as The boy wa too young and the young man was a hroni al holic hi h pre lud d inve tigation

Di cus ion

All 13 pati ts ffered from mal bsorption of varyi g severity and duratio All showed low o very low s rum i c con tration irre- pective of the dur tion of thei illness

A low serum zinc does not imply zinc deficiency per se but may be secondary to albumin deficiency for example (Walker 1973) Four of 13 patients w th malabsorption had unequivocally low albumin values and their low serum zinc concentrations can in part be explained by these low albumin values

None of the 7 women was receiving oestrogen therapy or contraceptive steroids or was pregnant at the time of the investigation - factors all of which are known to lower the serum zinc (Halsted 1968) None of the 6 men showed clinical signs of oestrogen activity

Rising steroid l vels cause a fall in the serum zinc (Henkin 1969) None of 13 patients was receiving steroid therapy or show d clinical sign of increased steroid production

Only one patient had increased orosomucoid concentrations indicating a chro ic inflammatory process None of the others showed clinical signs of inf ction at the time of investigation The serum zinc decreases secondary to inflammation (Burch 1975)

All patients had normal renal function and none showed proteinuria hypertension or oed ma

The investigations disclosed signs of malabsorption in all 13 patients du espec ally to hanges of the pro imal part of the small intestine and manife t as abnormal D-xylos -tol rance villous atrophy steatorrhoe folat deficiency and iron defici ncy defined as loss of bone ma row haemo id rin The defects happen to affect the part of the gut here the absorption of zinc and probably also of other trace minerals tak place

Investigations on uri ary excretion of zi c in 8 patients corroborate the suspicion of zı def ci ncy since the urinary zinc concentrations were ve y low Very low urinary xcretion of zinc has been reported i untr at d acrodermatitis enteropathica (Neldner 1975) With the method we used (Meret 1971) however it i possible that we underestimated the excretion of inc beca se the method does not involve acid d gestion of the urine samples. In any case the uri ary zinc excretion the e 8 pati nts wa considerably lower than re

ported normal values using this method (21 119 µmol/24 h Meret 1971) In two patients a marked incre s in inary zi was recorded aft r one week s oral zinc therapy

Plasma zi c concentrations lower than ormal have be n reported in patients with mal bsorption (Walker 1973) but o ignifica t d crease in u inary zinc e cretion could be demo strat d Th patient i the malab orption group showed e tirely differe t diagnoses from those in my seri s however: o ly 2 of 19 had coeliac d sease and several were suffering from inflammatory bowel diseas

In most of our 13 cases of malabso ption w th low ru zi o pl nation could be found othe tha inc d fici ncy

All 7 wome uff red from inf rtility in most cases of l ng sta ding Three had bee investigated gynaecologically but o planation wa found On woman conceived after the establishme t of gluten-fre diet and zinc therapy but aborted after 11 weeks

Two of three women with econdary inf rtility had pr iously given birth to i fants with congenital malformations and gave hi tory of prolo ged l bo They orre pond to ea li reports of mothers with bnorm l labour nd malformed inf t (I II)

Zinc defici ncy in xperimental f mal animals ofte give ise to infertility (Hurley 1966) but the e ct me h ism i n t k own Ex plan tion s gge ted i l de a d f ct i the DNA ynthesis (Fujioka 1964)

Addition of EDTA to the di t of f mal rat from the day of conception o severely dist rbed reprodu tion that one of the had gr ssly visibl i plantati site t t rm (Swenerton 1971) When the same EDTA s ppl me ts were give f om the 6th d y after conception ll the f ll term young showed gros ongenital malformations and marked red tion in birth weight These eff ts ould be pr ve ted by addi g 1 000 ppm of di tary inc From these res lts it ay be inf rred th t i rats t in is required t the time of i plan tation of the ovum and that the in req irement du ing pregna cy i great r than at othe time

Cyclic variations in serum zinc have been found in women (Höhn 1972) the highest concentrations being at the time of ovulation

Human subjects also how signs of altered hypophyseal function in zinc deficiency (Prasad 1966)

Gravidae that subs quently showed missed abortion had low serum zinc concentrations during arly pregnancy (II)

Three cases of i f rtility in women with coeliac disease who con ce ved after the establishment of glute free diet were never ex plained although it wa co cluded that vitamin B-12 def ciency and folate deficiency were not respo sible (Morris 1970) It seems that the likliest cause of infertility in human coeliac disease is zinc d ficiency

Zinc deficie cy rapidly results in degenerative cha ges in the t bu- l s of the testis in rats Correction of the def ci ncy is followed with n one week by reversal of the changes (Diamond 1971)

The male reprod ctive organs contain h gh concentrations of zinc (Vallee 1959) It seem possible th t zinc deficiency may influence the functio s of th se organs but the problem is outside the scope of th s vestigation

The thr e as of coel ac infertility (Foss 1962 Merianos 1975) may well be i keepi g w th the hypothesis of zinc d fici ncy

S mmary

Th rt e pati ts w th malabsorption 7 women and 5 men were in- vestigated e ten vely All showed low s rum zin concentrations irre pe t ve f the duratio of illness and degree of malabsorptio Eleve of the 13 had active coel ac di ea It was uspected that the low serum inc con ntration refl ted a state of zinc deficien- cy and this theo y a born out by the fact that no inflammatory reaction o l r ut albumin deficiency and no oestrogen or corti- coster d influ e could be demonstrat d All 7 women s ffered from infertility mo t of them of long standing Two showed seco dary infertility afte pregnancy and abnormal labour resulting i i fants

with congenital malformations (o e case of bilateral congenital dislocation of the hip and one of multiple c rdiac anomalies) I have reported similar complications in pregnancies in which the serum zi c was low

One of the infertile women conceived after the i stitution of glute free diet and zi c therapy but l ter aborted spontaneo sly

Investigations o zi c metabolism and i testin l bsorption might well prove valuable in otherwis nexplai ed inf rtility and co ld open up a new therape tic approach

LOW SERUM ZINC CONCENTRATIONS IN PREGNANCY RESULTS OF INVESTIGATIONS AND TREATMENT

By

Sten Jameson and Ingrid Ursing

Mothers with mature infants born by normal delivery showed significantly higher serum zinc during pregnancy than mothers whose infants were immature dysmature or were born by abnormal delivery (I II)

Seven of 10 women who gave birth to infants with congenital malformation had shown low serum zinc during pregnancy (I II V) A connexion between maternal zinc deficiency and congenital malformations in the offspring has been postulated (Halsted 1973 Sever 1973 Burch 1975 Hambidge 1975)

It was ot clear why some women showed low serum zinc concentrations d ring pr gn ncy but the low values were suspected to reflect zinc defici ncy (I II V) If this is the case it would be logical to ca y out therapeutic trials

Thi study was planned in ord r to investigate the reason for the low serum zinc co centrations in pregnant women and to examine the effects or oral nc sulphat supplementation

Mater l nd methods

Gra ida f r d to the Department of Medicine Regional Hospital Örebro owing to unsatisfactory haemoglobin concentrations in spite f rout ne treatme t with oral iron and vitamin supplementation were investigat d as out patients

Patients with rum zinc conc ntrations below 11 5 µmol/l were includ d in the t dy

During period of one year 20 women were found to f lfil this cr - terion

The standard i vestigation i clud d haemoglobin estimat o on capillary blood from the finger using the cya methoemoglob method; determination of serum zinc and copper on ve ous blood spirated f om a cubital vein using disposabl stainless needl s and acid- i sed glass tubes with plastic caps; estimation of serum vita i B 12 and folate; estimations of serum iro a d total ir n bindi g capacity (TIBC); bone marrow aspiratio ; and an lysis of i e a d fa ces

The zi c and coppe stimatio were do e by atomic b o ptio pectrophotometry The seru it i B 12 was do e by radioimmune assay

Folates were nalysed by a mi robiologic techniqu but we e not assessed if th patie t had eived f late b tit tion in pharmacological dosage which regula ly give ve y high serum fol te concentrations The serum i on and TIBC were analysed only if iron medication had been topped for 2 days

U ine was tested f the p ese ce of blood gl co protei and i trite Faec s were exami ed for haemoglobi

Bone marrow was spirated from corpu terni sme and cru h preparations were ined afte May-Grünwald-Gie s t ining

Bon marrow haemoside in wa estimat d a co di g to a e iquant t tive scal (I) The amou t of intra ll la d bris in bone ma ow ma ophages was e timated s miquantitatively (V) Two pati ts refused bon ma row aspiration

After compl ti g the inve tigation 8 wome were assigned t random to fu the investigation and tre tme t

Thi second i ve tigation wa done at one of the wards of the Department of ob t t ics nd Gynaecol gy nd l ted 10-12 days

S rum in d copper i / ri 24 h and oe t iol/ i 24 h were timat d The carbon monoo ide haemoglobin conc tration i blood

(CO-Hb) and the CO-concentration were measured after 2 days of abstinence from smoking The serum lactate dehydrogenase (LDH) bilirubin haptoglobin and reticulocytes in blood were estimated

The K^{+} Na^{+} Ca^{++} Cl^{-} creatinine chol sterol glucose aspartate amino transferase (ASAT) and alkaline phosphatase in serum (S-ALP) were measured S rum protein analyses were done by a special method (Ganrot 1972) using immunological techiques

A few blood samples were lost owing to technical errors

All pati nts were again given their ordinary iron and vitamin supplements after a short interruption for the investigation

Oral treatment with zinc sulphate 45 mg Zn^{++} twice daily was given in the form of an effervesc nt preparation Solvezinc[R] 1 x 2 After 7 days th serum zinc and zin /urine 24 h were measured once again Reticulocyte counts were done daily during the first 8-12 days of therapy Zinc sulphate therapy was maintained until delivery One of the 8 women was excluded from treatment a she planned to move from the district

The patie ts were regularly examined at the Antenatal Unit Data concerning durat on of labour blood loss at delivery birth weight of the infant and diagnosis were obtained from the records One woman was subsequently investigated in the 31st week of gestation owing to persist nt anaemia After stimation of plasma olume and total haemoglobin she received erythrocyte transfusions as during an earli r pregnancy

Stati tic l a alyses were done by mean value analysis and Student s t-test for single and paired observations

Results

Thi teen of 20 omen showed haemoglobin values be ow the theoretical l mit for ana mia (WHO 1972) See

	mean	SD	SEM		range
Haemoglobin g/l	103 1	11 8	2.6	20	76 - 118
S kobalamin pmol/l	300	231	51	20	114 - 1180
S folate nmol/l	28	12	4	12	8 45
S iron µmol/l	18	7	2	12	9 37
S-TIBC µmol/l	86	14	4	12	62 - 110
Mac ophage gradi g	2 6	0 6	0 2	18	1 3
Duration of labour h	10 7	10 3	2 4	19	1 5 - 47
Blood loss at delivery ml	463	469	105	20	40 1500
I fant weight kg	3 48	0 60	0 13	21	2.04 - 4 41

Tabl 1 Mea s and ra ge of haematological data and dat con c rni g labou blood loss d i fants birth weights In one cas cae rean se tion was done aft r 8 hou s listed a labour See Fig 1

All 20 showed normal serum vitamin B-12 and 12 women that were not treated with pharmacological folate substitution showed normal folate concentrations None of 18 women investigated showed megaloblastic disturbance of cell maturation in bone marrow

Nine women lacked bone marrow ha mosiderin and one showed only traces; 6 of 18 showed subnormal values of bone marrow haemosiderin

In 17 of 18 women there were many or very many cell fragments in the cytoplasma of the bone marrow macrophages (V)

In 7 of the 13 women with anaemia (by def) no clear explanation of this low haemoglobin value was forthcoming All 7 showed normal se rum vitamin B 12 folate deficiency was not probable bone marrow preparations were not megaloblastic and bone marrow haemosiderin could be demonstrated

All 20 wome showed normal urine analyses and none of them had signs or ymptoms of faecal blood loss

Serum protein an lyses howed one low albumin value (31 g/l) in one of 8 patients One other showed a rai ed orosomucoid concentration (Table 2)

No sign of haemolysi such as haptoglobin elimination increase in serum bil rubin or LDH or reticulocytosis were found High CO-Hb concentratio or i reased CO percentage was fo nd in only one woman and she had probably been smoking (Table 3)

Two of 7 pati ts showed low serum iron high TIBC and low saturation indi ati g iron deficiency

The serum K^+ Na^+ Cl reatinine chol sterol ASAT bilirubin and glucose were ithin the normal limits of the laboratory and have not been recorded The erum alkaline pho phata and calcium did not differ from normal pregna cy values (Table 3)

pati nt o	S protein g/1	S-albumin g/1	S IgG g/1	S-IgA g/1	S haptoglo-bin g/1	S-orosomu coid g/1
1	66	41	12 6	2 3	1 0	0 9
2	61	42	8 8	1 8	1 4	1 3
3	66	39	7 6	1 8	1 2	1 0
4	59	41	6 6	1 5	0 8	0 8
5	62	35	5 8	1 0	0 7	1 8
6	72	44	7 3	1 9	0 9	1 0
7	61	39	7 0	0 9	0 6	0 7
8	61	31	7 2	1 7	0 7	0 8
normal range	65–80	40–52	7 14	0 8–3 0	0 3 1 6	0 5–1 4

Tabl 2 The distribution of serum protein concentr tions fro 8 gra idoo and laboratory s normal range

patient no	CO-Hb %	CO vol %	LDH µkat/l	S-bilirubin µmol/l	S-Ca mmol/l	S-ALP µkat/l	reticulo cytes o/oo	haemoglobin g/l
1	0 88	0 13	-	6 8	2 4	6 4	7	97
2	0 50	0 06	7 6	5 1	2 4	4 7	4	80
3	0 80	0 12	5 3	5 1	2 4	8 0	3	112
4	0 94	0 14	5 0	5 1	2 3	4 7	11	100
5	0 10		5 9	6 8	2 5	3 7	5	92
6	0 89	0 12	5 0	13 7	2 4	-	12	93
7	3 80	0 60	4 4	10 3	2 2	9 8	13	118
8	0 80	-	6 9	8 6	2 2	6 4	3	76
normal range	< 1 1 %	< 0 2 %	3 8-6 7	3-20	2 2 2 6	2 0-5 0		

Table 3 The distribution of blood data concerning 8 gravidae Normal ra ge of CO-Hb and CO in blood conc rns non smokers or smok rs after > 24 hours of abstinence Abbreviations are xplained in text

One of 8 wome showed raised oestriol excretion for the week of gestation in question nd gave later o birth to t i s The other 7 showed excretion within the normal limits of the l boratory (Tabl 4)

Patient no	S zinc µmol/l	one week s treatment	tU zi µmol/24h	one we k s treatment	tU-oestriol µmol/24h
1	8 2	9 8	8 9	13 8	57 2
2	8 1	15 0	2 3	17 3	20 5
3	10 1	10 1	2 0	6 1	41 3
4	8 2	10 1	10 9	16 1	72 9
5	11 2		5 0	15 3	41 6
6	8 3	10 9	7 4	8 7	34 7
7	7 7	10 1	6 7	15 8	62 5

Table 4 S rum inc o ce t ation and rin ry zinc e cretion before d fte one we k s i c lphate t eatment and u inary oestriol cretion in 7 gra idae T tests for paired observations ser zinc t 2 69 $p < 0\ 05$ uri ry inc t 4 07 $p < 0\ 005$

Zinc cretion in rine was low i 11 8 cases and considerably lower than what has been r port d as normal u ing this method (21) 6 119 2 µmol/24 h Meret 1971)

All 7 women that rec ived oral zinc s ppl ments showed increas d urinary zinc e cretion after one week s treatme t ($p < 0\ 00^{r}$) indicating that zinc had been absorbed (Tabl 4)

Five of 6 pati t also showed an i c ase in serum zinc aft r one week s zinc treatme t ($p < 0\ 05$)

Zinc treatme t did not bring about reticulocytosis during the 8-12 days the pati ts wer followed p

Patient no	Age years	pregnancies	parity	week of invest	week of delivery	S-zinc µmol/l	S-copper µmol/l
1	18	1	0	35	40	8 2	26 7
2	25	2	1	27	41	8 1	42.4
3	27	2	1	35	42	10 1	33 0
4	25	3	2	30	38	8 2	30 9
5	18	1	0	27	42	11 2	-
6	28	4	3	27	40	8 3	23 6
7	32	2	1	33	39	7 7	37 7
8	25	1	0	31	41	7 0	29 8
9	35	2	0	31	42	10 7	38 5
10	40	5	3	29	41	11 0	34 9
11	27	2	1	34	41	10 7	-
12	24	1	0	32	40	8 4	42 4
13	30	3	2	33	43	10 4	28 3
14	22	3	0	27	43	10 6	28 3
15	23	3	0	26	44	10 7	-
16	26	4	1	37	40	8 6	30 9
17	26	3	1	32	44	9 0	37 7
18	25	3	1	28	41	10 7	33 0
19	18	1	0	32	40	9 3	31 4
20	23	2	0	24	41	10 4	38 9

Table 5 Data concerning 20 gra idae with low serum zinc Patient no 1 7 were treat d with zinc sulphate

Three of 7 t ated women lat r stated spontaneously that their sense of tast had improved One woman complained of naus a one hour aft each do of zinc but no other sid effects were noted

The findings concerning duration of labour blood loss at delive y and birth weights are listed in table 1

Seven women treated with zinc s lphat had normal deli ries b t i one of them a primigravida duration of labour was 24 hou (Fig 1) and her infant showed slight signs of dys at rity She had r ceived the briefest zinc therapy (5 weeks) Two women were delivered of or mal infa ts in the 42nd week and one woman gave birth to i matur twins in the 38th week (T ble 5)

Five of 13 women who did not receive zinc therapy had ormal delive ries Five of these 13 women we e delivered i the 42nd we k or l ter and 4 of the infants were dys tur Compli tions of abnormal deliveries are listed i t ble 6

	n
Partus protract s + positio ab- normi fet s + VE	1
P compl pos abn f tus + p o- l ps s funiculi + CS	1
P compl po tmat itas f t + CS	1
P c haemo rhagia atonica i p + blatio plac ntae partiali	1
P c retentio plac part	1
P protractus compl + haemor hagia atonica post partum	1
F praecipit t gra pr long	2
	8

Tabl 6 List of complications t d livery concerni g 8 of 13 gra id who re- ceived no inc tr tme t VE = vacuum xtraction CS ca rean section

	mean	SD	SEM	range	n	normal range
Age	24 9	4 0	0 7	18–34	33	
Week of examinatio	25 4	5 7	1 0	14–35	33	
Haemoglobin g/l	100 1	7 8	1 4	76–109	33	> 110 g/l
S-zinc µmol/l	11 5	2 1	0 4	7 0–15 3	33	13 2–20 0
S-copper µmol/l	33 1	4 7	0 9	21 3–42 4	31	13 0–26 0
S-kobalamine pmol/l	236	91	16	96–619	32	100–750
S-folat ol/l	28 4	12 7	2 5	7 5–45 4	26	7–34
S-iro µmol/l	19 1	5 8	1 8	10 7–30 1	10	12–30
S-TIBC µmol/l	85 4	15 3	4 8	62 3 109.5	10	45–80

Tabl 1 Age distribution week of examination, and blood findings in 33 pregnant women with refractory anaemia

Among 33 wome the bone marrow haemosideri was absent in 18 pre- s nt i trac s in 5 subnormal in 7 a d normal in 3 In 30 women bone mar ow macrophages were present in increased nu bers and showed i cr sed amou ts of celldebris (grade 2–3) This grading is significantly higher (p < 0 001) tha in on-anaemic primigravidae (I) s e Table 2

The 33 wome showed som what lowe bone marrow haemosideri values th 83 on-anaemi primigravidae (I) (p < 0 05 Table 2)

Celldebris in macrophages grade;	1	2	3	n	t	p
anaemic gravidae;	3	7	23	33		
non-anaemic primi-					4 88	< 0 001
gra idae;	44	14	25	83		

bone ma row haemo-siderin grade;	0	tr ce	I	I II	II		t	p
anaemic gravidae;	18	5	5	2	3	33		
on-anaemic pri							2 08	< 0 05
migra idae;	17	27	24	9	6	83		

Tabl 2. distributi n of bone marrow ma rophages and thei ont t of cell debris grade 1-3 i anae ic gravidae a d non-anaemic primigra idae Distribution of bone marrow ha mo-sid rin according to same groups and t-t sts

Two women showed low serum itami B 12 conce trations and in on of them the bon marrow cells showed a megalobl sti ch ge

Three wome showed a low serum fol te and i the pati t with the lowe t value the marrow howed a megal bl tic appearanc

Thes two women with megalobla ti marrow cha ges showed the lowest inc concentrations of 33 wome

All but two of the 33 wome showed low s rum zinc co centrations in relation to the week of gest tion and to the distributio of mean inc concentration i 234 gravid (II) Figure 1

Eight wome showed i c conce tration lower th n 2 standard devia-

tions for this series (II)

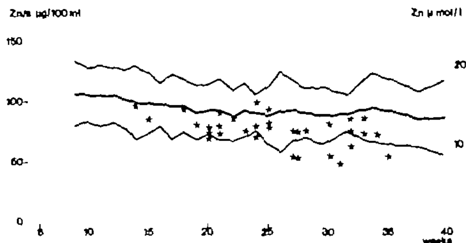


Fig 1 The distribution of erum zinc values (asterisks) from 33 naemic gravidae according to week of gesta tio compared to th *distribution of means* ± 2 SD of 493 s rum zinc readings from 234 gravidae (II)

A significant differ nce in Serum zinc concentration was found betwee the 33 wome of this series and those in no -anaemic primigravidae ($p < 0.001$) *and this differenc in zin concentrations* is much greater than would be expected from the difference between the groups according to duration of gestation (Table 3)

The serum copper co centrations however *are lower in the* s 33 women than those in primigra ida ($p < 0.02$) No frankly *high values* were recorded in the a aemia group (Table 3)

S zinc µmol/l	mean	SD	n	t	p
anae ic gravidae	11 5	2 1	33		
on-a aemic pri-				9 05	<0 001
migra idae	15 4	2 1	80		
S-copper µmol/l					
anaemic gra idae	33 1	4 7	33		
on-ana mic pri-				2 45	<0 02
igravidae	36 4	6 9	78		
S folate nmol/l					
anaemi gravida	28 4	12 7	26		
non-a aemic p i-				2 46	<0 02
igravidae	22 7	9 6	83		
S-kobalamine pmol/l					
anaemic gravidae	236	91	32		
non-anaemic p i-				0 45	<0 7 N S
igravida	244	80	83		

Tabl 3 Mea o cerning S in S-coppe S fol te and S kobalamine and t-tests te ti g the significance of diff rence between g oups f anaemi gra idae and on-anaemic primigra ida

Th serum vita in B-12 val s did not differ significantly between 33 aemic gravidae and no -anaemic primigra ida (p < 0 7) Th s ru folat wa highe in anaemi gra ida than i non-anaemic primigravidae (p < 0 02) tabl 3

Twelwe of th 33 wome gave birth to mat re i f t at normal term by normal d livery

Partu iton curred in th 42nd week o lat r i 8 cases

Premat re delivery occu red i 2 t i pregna ci s both with two im-

mature infants

Three infants were dysmature One boy showed a large naevus flammeus faciei

Eleven labours were complicated (for details see Table 4)

	n
Partus protractus (2) + VE (3)	5
P compl c asphyxia fetus imminens + CS	2
P c retentio placentae	2
P c haemorrhagia atonica intra partum	1
P c haemorrhagia atonica post partum	1
	11

Tabl 4 Complications during delivery VE = vacuum extraction CS caesarean section

Altogether 21 of the 33 women gave births to immature dysmature or malformed (one case) infants and/or developed complications during delivery or were not delivered at normal term

Discussion

The 33 anaemic gra idae are a highly selected group The criterion of selection was an unsatisfactory response to routine oral iron-vitamin medication with physiological amounts of vitamin B-12 and folate and in many cases pharmacological doses of folate With this selection the series would come to consist of patients with anaemia due to causes other than ordinary iron vitamin B 12 or folate defici ncy

In spite of curre t and earlier treatment 23 of the 33 women showed no bone marrow haemosideri or only traces suggesting that the anaemia was essentially due to iron deficiency The 33 women also showed

some hat lower bone marrow haemosiderin values th 83 non-anae ic primigravidae

In a seri s of non-anae ic iron treated gravidae only 33 % how d st inable bone marrow haemosiderin during the latt r part of pregnancy (Svanberg 1975) The value of bone marrow haemoside in estimatio s i the diagnosis of iro defici cy whe iron turnover is apid have been disputed (Norrby 1974 Svanbe g 1975) Others consider marrow haemosideri estimatio s to be of most value i evaluating the early stages of iron-defici nt erythropoie is (Finch 1970) A decreas in or abs nce of bone ma row haemosideri s also t invariable fea ture or i on deficiency (Fairbanks 1972)

Among 33 naemic wome only 2 showed megalobla ti cha ges i bone marrow cells and the 2 wome also showed the lowest serum zinc

Low s rum inc concentrations h ve bee reported in untre t d perni cious anae ia (Vikbladh 1951) and have been found to be ome ormal within 4-7 days aft r instit tion of pecific therapy with l ver pre parati ns This phenomenon may be hange that happe to d vel p at the same time a the an e ia ithout t ologic l conne ion but it could also be a sign f mal bs ption If low rum i c was a ign of defi i cy this deficie y might ont ib te to a dete iora tion in haematopoi tic cell maturation

The s rum vit in B-12 value did ot diff betwee 33 anaemic pregnant women a d non-ana i p imigrav dae and serum f l t wa higher i anaemic wome This to be ff ct of prophylactic admini stration of these vitami

Bone ma ow macrophages showed incre s both i number and i cytopl smic conte t of cell d b is in 33 aemic gra ida The findings may be int rpreted sign of phagocyto i of def t cells and is not ee in bone marrow preparation from persons ith normal blood production

These gradings of cell debri i bone ma row macrophages in 33 anaemi women were ignificantly higher than in on-anaemic primigravida ($p < 0.001$) A correl ti ha bee found between this g ading

of bone marrow macrophages in patients with haemolytic anaemias and different degrees of intramedullary haemolysis (Jameson 1974) Haemolysis was measured as increase of serum lactic dehydrogenase (LDH)-activity corrected for intravasal haemolysis, or carbon monooxide (CO) production

No signs of haemolysis such as haptoglobin elimination LDH increase CO-haemoglobin increase or reticulocytosis were found in 8 women with lo serum zinc however (IV) It is possible that these features of haemolysis are too insensitive in this respect LDH is a zinc metalloenzyme and lowered activity of this enzyme has been reported in tissues of zinc deficient animals (Prasad 1967) The activity of ALA-dehydratas is increased by oral zinc supplementation in man (Abdulla 1971) If haeme-synthesis were impaired by zinc deficiency damage to this synthesis would affect the ALA-PBG step and CO-production would therefore not be affected

Zinc seems to ex rcise a stabilizing effect upon cell membranes (Chvapil 1973) I model experiments on haemolysis an inverse correlation between grade of haemolysis on the one hand and dietary zinc conte t and erum zinc concentrations on the other was found (Pfeifer 1971)

Two one of the 33 showed serum zinc exceeding the mean during that week of gestation hen they were compared ith 234 other gravidae (II) The woman who showed the highest serum zinc showed also the lowest grade of cell debris in bone marrow macrophages Most of the 33 wome showed low zi c concentrations however and in 8 of them these were lower than 2 SD (Figure 1)

It was fou d that s ch low zinc concentrations were not secondary to albumin deficiency or inflammatory reaction (IV) to extra high oestrogen retion (II IV) or to e tra high serum somatomammotrophin conce trati s (II) It seems also unlikely that these low figures for zi c were secondary to high copper concentrations as these 33 women sho d serum copper concentrations slightly below those in non-anaemic pr migra idae (Table 3)

It cannot be established for certain hether abnormal plasma volume

expansion co tributed to th low zinc co c ntratio s

A high incidence of complications was found among the 33 women All had received iron s ppl ments by mouth and oms l o i t amuscular ly afte investigation All that showed marginal vitami B-12 a folate conc ntratio s received these sub to ces in pharmacological do es

Severe anaemia in pregnant woma increa s maternal morbidity and i - volves a higher risk to the fetus (Gatenby 1960 Ll wellyn-Jones 1965)

Low serum zinc conce tratio seem also to increase the risk (I II IV) These findings ar corrobo at d by this s ri s of 33 gravid e with refractory aemia and in most cases (31/33) also low seru zinc concentrations

An aeti logical conne ion betwee anaemi d low serum zi seems pos ibl The finding of large amou ts of c ll d b i i bone ma row macrophages may be int rpreted s a onseq nce f increased i trame dullary cellde tru tion which i t rn may be secondary to a d fi- cie cy situatio with p od ction of lls with un t bl me branes (Chvapil 1973) or othe defects Some onnexion with impaired haeme- synthe is owing to a def ct in ALA-dehydratase ff t (Abdull 1971) may also be possibl Zi s pplement t o au ed no retic locytosis within 8-12 days (IV) but this obs rvation pe iod was prob bly too short

In rd r to lucidat thes que tions still f rther a pro pective study has bee started in whi h every s c nd pregnant woma with low serum in i treat d with i c lph t The res lts re not yet complet

Summary

Thirty thr gravidae with naemi in pite of iro and vitamin supp- leme t tion were xamined d 31 were found to have low or very low serum inc conce trations with regard to the we k of gestation Twenty-thre f the 33 howed no bone ma ow haemo ide i or only trac Thirty showed mod rat great i rease in i trac llula

cell debris in the bone marrow macrophages indic ting an increase in intramedullary cell destruction Two women showed low serum vitamin B-12 or folate concentrations and they also showed lowest zinc concentrations recorded in the ser es

Twelve of the 33 women gave birth to mature infants by normal delivery; 21 developed complications during labour or gave birth to immature dysmature or in one cas malformed infants and/or were not delivered at ormal term

Low serum zinc in pregn nt women increases maternal morbidity and involves a higher risk to the fetus

It is suggested that an aetiological relationship ex sts between low serum zinc concentrations and refractory anaemia of pregnancy resulting in increased intramed llary cell d struction This effect might be aggravated by iron d ficiency

GENERAL SUMMARY

The results prese ted in these studies (I–V) ar as follows The serum zinc falls gradually during first and second trimest r Vari tions in serum zinc in the i divid al healthy pregnant woman are small

A s l cted group of normal gra idae who subsequently gave birth to normal infants by normal delivery showed a slow gradual fall i serum zinc concentrations and showed no abn rmally low recordi gs

Women delivered before or after normal t rm showed lower zinc concent rations during early pr gnancy than women delivered i the 40th we k Women with abnormal deliveries especially ineffici nt labour and atonic bl eding showed lower erum zinc concentratio s during early pregnancy tha women with normal deliveries

Women who gave birth to immature or dysmature infants showed lower seru zinc conce tration du ing early pregnancy tha wome with no mal deliveri s and rmal i fa ts

Ten infants showed congenital malformations Six of thei mothers had shown the lowest figures for serum zinc recorded d ring that particular week f ge tation in two s ries of gravidae (82 + 234 cases) Gra idae wh subsequently developed missed abo tion showed lower serum in co centrati s tha gra idae who aborted sponta neou ly The serum i c was low among patie ts with malabsorption st tes especi lly coeli c dise S ve coeliac wome showed in- f rtility of lo g standing Two f them showed secondary inf rtility afte givi g birth to malformed infants by b rmal delivery

Gravidae with refra tory anae ia showed strikingly low seru zinc and igns of increa ed intramedullary cell destruction

Oral i c lphate therapy increased serum zinc concentrations and inary cretion of inc and seemed to have a ben ficial eff ct pon l bou and augme ted taste acuity in some cases

Serum zinc concentrations were not corr lated to haematological factors such as haemoglobin serum vitamin B-12 and folate concentrations or amounts of bone marrow haemosiderin

No correlations between serum zinc s rum somatomammotrophin or urinary excretion of oestriol were found

These results are strikingly similar to earlier findings concerni g the effects of experimentally induced zinc deficiency in animals

Low serum zinc concentrations during human pregnancy may be a sign *of zinc deficiency implying risks to mother and infant*

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From Medical Department B Rigshospitalet
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Mitral Regurgitation

Description of a method for quantitative determination of regurgitant flow with hemodynamic and clinical correlations

By Kjeld Lyngborg

This thesis has been accepted by the Medical Faculty of the University of Copenhagen to be defended in public for the degree of Doctor of Medicine

Copenhagen
January 22nd 1976
J C Melchior dean

Denne afhandling er af det lægevidenskabelige fakultet ved Københavns Univer itet antaget til offentligt at for svares for den medicinske doktorgrad

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Contents

CHAPTER III

Preface

The present investigation was carried out in the Cardiovascular Laboratory of Medical Department B, Rigshospitalet (University Hospital), Copenhagen during the period 1964-1968; the results were analyzed further during the following years.

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Introduction

The aim of th pr sent investigation i to describe and evaluat an indicator di lution method for det rmination of mitral gurgitation and to exami e th re lationship between clinical and h modynami finding and the degree of mitral regurgitation determined.

In thus study mitral r gurgitation mitral insuffi ie cy and mitral in comp t nc have been sed s synonyms

F r practical reason se has been m de f abbrevi tions and symbols these are listed and explained in th back of thi book (p 220 222)

The statisti al analyse we carried out by the st tistician f Rigshospitalet, J Nyboe cand act. Th data w e analyzed s ng the computer at Rigshospita let [1]

Fo the purpose f describ ng th sult a group the r thmeti mean and stand rd devi tion have g ne ally been ed How v for the purpose f statis ti al testing non p rametr method w mployed To test the hypothesis the 2 o more sample re drawn from th same popul tion, a against the hypothesis that they com from population with diff rent locations, rank sum tests such a th Wil o t st (f p ired ob rv ti s) th Mann Whitney test (for indep d nt ob erv tions) and th Kruskal Wallis t st w used T examine whe or not two var able are rel ted th test b sed on Sp arman s rank corr coeffi t w s used

[1] CDC 3300 from Control D ta Corporation, M nneapolis, 55440 U S A

Chapter I
Historical aspects*)

Description and diagnosis of a disease are dependent on the diagnostic methods available to the physician in his time (table I 1)

T ble I 1 Mileston s in cardiac diagnosis

P lpati f pul	Imh t p	2700 B C	
P lp ti n f h t	Alb tini	1726	
P r i	A nb ugg r	1761	
St tho opy	L n c	1819	
R tg min ti n	R ntg n	1895	
El ctr di gr phy	Einth	1903	
H t th t i ti	F sma – C rn nd	1929	1941
A gi di gr phy	C t ll n s t l R bb d St i b g	1937	1938
Ult d di gr phy	Ed l nd H t	1954	

Palp tion of the rterial pulse i probably the arliest method employed in the examinati n f h art diseas It was used by the an ient Egyptians Hippokrat s Gal n and the P rsian physi an Rhaz z (Willius and Dry 1948) A

*) In preparing th review the wo ks of th following authors have been drawn upon: Warburg 1931 Roll ston 1941 Williu and Key 1941 Herrick 1942 Wil liu and Dry 1948 Brigden nd I eatham 1953 McDonald et al 1957 White 195 Veer 1958 Selzer and Katayama 1972 Bedford 1972 Godtfredsen 1975

proper und rstanding of heart disea w hindered for centuries by Gal n s misconcepti ns of the circulatory system and it function; the work of Harvey (1628) and Malpighi (1661) provided a orrect description of the circulation and thus of the function of th heart (Willius and Dry 1948) Until the invention of th steth scope by Laennec in 1819 few possibil ties were available for the diff ential diagnosis of heart disease in vivo parti ularly r garding valvular diseas The development of the lectrocardiograph by Einthoven in 1903 mad it po sibl in clinical practic to d scribe and cla sify ar hytmia and myocardial disease Investigations using model and animal xperiment were part of th 19th entury surg of inter st in physiology C theterization of th human heart was first carried out by For smann in 1929 this wa m de routine procedure by Cournand and Range in 1941 and brought about a revolution i cardiac diagnosis when mbined with th technique of angiocardiography (Castellan Pereiras and Garcia 1937 Robb and Steinb rg 1938) the latt r technique presupposed the discovery of roentgen rays in 1895 roent g n examination of th heart w ctually carried out already in 1896 by William (Willius and Dry 1948) and i in itself an indispensabl tool in car dio diagnosi Ultrasound cardiography (Edl r and Hertz 1954) belongs to the inventions of thi entury recent imp ovem nts of a techni al nature sugg st th t thi m thod of examination will becom a routin procedur in most cardiovascular laboratori s.

Although the in vivo diagnosis f valvular heart dis as w in fact impos sibl before L ennec inv ntion (Laennec 1819) diagnosi was still possibl at autopsy Autopsy w s in reality carried out by th ancient Egyptian r sult of their p a tice of mummificatio of bodi s (Williu and Dry 1948) but it w s not generally perf rmed in the M ddle Age (Godtf edsen 1973); in 1315 however an autopsy wa arried out in Bologna by Mondino de Luzzi called Mundinus (Godtfred en 1973) Autopsy wa rarely performed in th 14th century but gradually becam more comm n throughout the 15th and 16th entury; a systematic study f path logi al anat my first appeared in 1761 D sedib s et usi morborum p an t men indagati by M gagni (Godtfredsen 1973)

M tral st nosi w d scribed s arly 1668 by Mayow (Mayow 1668) and de ribed agai by Vieussen in 1715 (Vieussens 1715) Bo et in 1672 described patient dying of aortic sten sis (Hansen 1967) A rti insuff ciency w s fi st d scribed by Cowp in 1705 (Cowper 1705) Both thi utho and V eu sens (1715) had clear unde standing of valvular regurg tati a m jo abnormal ty

To my knowledge Sena in th first textbook of cardiology T aité d l structure d oeur de son ti n et d se mal di s was the first to describe m tral insufficiency I man who w subject t dyspnoea, th l ft v ntricle w xtraordinarily nl rged th olumns and uricular valves wer sified the l ft auri le appea ed to hav enl rged vity th contracti ns of the heart could send th blood strongly back to th t v ty the valve neve cl sed the en tranc to that v ntricle th y w re ttached to th wall their o sif cations not permitting th m to lev t (S na 1749)

C rvisart ndoubtedly knew f Senac work and in hi clini dilation o insuff ncy f the (a culov ntricular) opening w s cl ssif ed a disease s i apparent from hi aphor sms (McDonald 1939) Corvi art ecognized the disea e wh inst d of feeling s th ill on is co scious of tumultuou disturb ance H w s also clearly war f th h modynami mechanism Thi (disturb ance) ari es from the f t that at ch ontraction of the ventricl a portion of the conta ed blood f rced back into the uricl at the same tim blood is coming from the l ng through the auri le t nt r the ventricle Corvisart himself was th first t desc ib ruptur of the chord t ndi e of th mitral valve (Corvis

art 1806) His assistant Merat had even earlier reported a case with a ruptured left ventricular papillary muscle (Merat 1804)

Table I 2 Milestones in the history of mitral insufficiency

Cu pid l mitr l insuffici n y	S c	1749	
Rupt r of p pillary mus l	M t	1804	
R pt of th chord tendi e	Corvisart	1806	
M rmur f mit al in ffi iency	H p	1833	
Mod l inv tig tions	v B ch	1892	
Phy i l gi l inv stig ti ns	Wigg r d F il	1922	
V w ve in wedg t aci g	L g rl f and W rk	1949	
Angi rdi gr phic dem n strati n f fl x	Smith t al Pri ton	1956	1957
Operation f h rda t ndin rupta	McGoon	1960	
V lv pro th i	Starr nd Edwards	1961	
P pillary mus le dysfun ti n	Bu h Pasqu l d Phillips	1963	
Bill wing valve sy dr m	Ba low and othe	1963	

The murmur of mitral insufficiency was not described by Laennec who obviously heard and recognized the murmur of mitral stenosis ("the sound which attends the contraction of the auricle becom s much mor prolonged more dull and with something in its tone which reminds one of the rasping of file on wood and sometimes of a bellows smartly compressed" (Will us and Keys 1941)) but misinterpreted its timing as he thought that the second heart sound wa *due to auricular contraction (the second heart sound was first* proven to be due to the closure of the semilunar valves in the middl of the 1830s (Williams 1835))

The murmur of mitral r gurgitation was first described by Hope in 1833*) When the (mitral) valve is permanently patescent adm tting of regurgitation, the first sound is attended with a murmur These murmurs are louder opposite to the mitral valve (viz at the left margin of the sternum) between the third and fourth ribs about three or four inches above the point where the apex of the heart beats, than elsewher Williams (1835) however disagreed on the point of maximum intensity of th murmur as he heard t best more to the left a about the nipple r a little below it Som confusion in the interpretation of the mur

*) The prefa of Hope s book dated 1831 Elliotson (1830) preceded Hope by 3 years in describing r gurgitant auri ulo-ventricular murmur but he de scribed only s having tricuspidal insuffi ency

mur continued t be pre nt for some time (Stokes 1854 With 1858) Howeve the clear and systematic approach to auscultation by Austin Flint (1859) would have enabled the attentive reader to diagnose mitral regurgit tion (as other valve di e s) wh n the typi al murmur was pre ent.

The evaluation of mitral insufficiency howeve w s to chang much in th following century particularly regarding th interpretati n of an apical systolic murmur Hope (1833) already noticed that Bellows-murmur a already fully explained, sometimes exists in the heart though th re be no disease of the valve Austin Flint (1859) sked I it tru n the other hand, that a systolic murmur ef rabl to th mitral orific unif rmly denot the exist nce of insufficiency egurgitation?" and answered himself Thi questi n must be answe ed in the negativ in nly a rtain proportion does regurgitation occur and went on to describe the circumstances where regurgitation was most likely; h also in hi tre tise described Inorgani murmur Balfour (1876) similarly stated that systolic apex murmur is by no mean alw ys a certain proof of any p sitiv derangement of the cardiac mechanism H d scribed two typ s of mitral egurgitation: curable mitral regurgitation with chlorosis nd febril disease exampl and incurable mitral r gu gitation a egurgitation depending on ctual disease f the mitral valv hi views on the latter are not quite cl h regarded an pical systolic murm r a a sign of mitral st nosis

Broadbent and Broadb nt (1900) used 22 pages of th ir textbook n heart di se to describe th signs of mit al regurgitati n and the differential diagnosis also regarding mitral incompetenc without dam ge t valves Th difficulties in m king prognostic evalu ti n are also described. The range of po sibilities regard durati n of lif mitral regurgitation due to ctual damage f the valv by cut ndocarditis l m re extensiv than in any th f m f valvular dise se

St l (1906) was scepti t the significanc of mitral regurgitation. In the preface of hi textbook n h art dise se (Steel 1906) he quoted his pathol gist for the following At your sugg stion I hav gon ove the postmort m not of your se fo th p st few years. It is markabl that out of the ry large numb f cardi c case examined v ry considerabl number being ample of mitral st nosis I hav hardly been bl t elect ngl e f what you might call straight forward m tral incompetenc f om mitral lesion pure and simpl Steel (1906) found it impo sibl to give descripti n f f mitral incompet nc mitral incompet nc ccur under such an imm se variety f nd tions many f which it i far from being th essential fe ture f th pathologi al proc s Oft n it is qu t unimportant one Of the ar st nditi n structural hange in the val curtain f natur alcul ted t ender th m incompetent septic ndocard ti furnishe th b st xampl Then om the much more com m but gre tly le d stru t v heum tic endocard ti Mitral im mpet nc xceedingly c mm oncomitant f mitral st nosis Th t th gu git tion und th ircumstance i f any great importanc m v w ll b doubted

Th views of Mack nzie (1916) o mitral insuff ency were dramatically ex pre ed and nfl nced phy icians fo years: Mi tral regurgitation even from a damaged val ldom if ev f much mportanc It is doubtful whethe m tral incompetenc ever onstitut serious embarra ament to the heart I c n fully nd rs G aham Steel dictum that no one ever di from

mitral regurgitation He described the onsequences of auscultation (' this un trustworthy observation) and is probably mainly referring to the d scription of api al systolic murmurs: Perfectly healthy men are today being rejected for the Army or invalided out of it because of a murmur has been detected in their hearts. Others who pres nt themselves for life insurance are r jected or mad to pay a higher premium for the same reason, while innumerable individuals are subject ed to prolonged tr atment and great restriction in their mode of lif because these ea ly superficial observations have misled the profession At time physic ans of experience will admit that certain murmurs may not have a serious significance in saying this many f them ppear to imagine that th y have made an important c ntribution to th subject But having failed to point out at the same time how a murmur can be valued so as to discove when it is of signifi ance and wh n it is not, they h ve really failed to carry forward our knowledge in any respect *) It is p obable that too many p tient we e at that time registered as having mitral insuffi iency Guttmann (1891) as well a Fastianoff (1910) reported pure mitral insuffic ency to be th m st common type am ng th valvular lesions (39 and 45 per cent espectively) thi could possibly be due to the t achers of students being mo e enthusiastic in diagnosing significant mitral r gu gitation than recommended by the textbooks

> Cabot (1926) continued th tradition of Mack nzie (1916) by using as title of a passag th following Mitral Regurgitation, Doe it exist?" and answered this question by reporting that among 1846 necropsies of heart patient only 7 cas s of mitral incompetenc were found three of which we m r o 1 as doubtful **) H further ommented But granting that mitral r gurgi tation probably exists as a great rarity, it is not a clinical entity for it an not, so far I see b recognized in lif

Mitral insufficiency ontinued f r s me time t be egarded f little importanc by some author Lewis (1942) concluded Briefly th diagnos s of mitral regu gi tation has a very limited importance but added A suredly if th diagnosis of regurgitation m tter qua egurgitati n, t m tter acc ding to d gree

The tide had alre dy changed Mod l experiments e e rly s 1892 (v B ech 1892) and particularly the animal experim nts f Wigg rs and Feil (1922) h d d monstrated that mitral regurgitation ould au signifi ant ha modynami hanges (experim ntal investigati ns are furth d cribed in hapt r IV) Clinically Spragu and White (1926) descr bed 20 c es of p r mitral regurgitation and re

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*) A een from the oth auth rs mentioned above descripti ns of the pi al ystoli murm had actually be n given arli w th regard t both it diff r ntial diagnostic and ts pr gn stic s gnifi ance

**) It is actually surp ising th t Cabot (1926) as well a Steel pathologist (Steel 1906) were unable t find m r ase of mitral egurgitation t autopsy Other fact rs howev may account f this all es having d formity or some narrowing of the mit al valves we e probably registered as mitral stenosi although mitral regu gitation may have been th significant haemodynami ev nt and not mitral sten sis. Furthe more both studie wer r trospective and not especially aimed at demonstr ting mitral egurgitation, which i diffi ult to demonstrate at the autopsy table and demands time and interest.

ported that th left ventricl was found by roentgenological examination to be en larged in half of th e cases; they oncluded th t a loud ap cal syst lic murmur could not be entirely disr garded. Pure organic mitral regurgitation i a clinical ntity but it is not d monstrated at autopsy as it is rarely if ever f tal. R gurgitati n i usually but on stag in the p ocess of stenosis, which is m re often th terminal condition Boone and Levin (1938) d scribed 59 case h ving a grade 2/6 o more apical systoli murmur 25 of th se lat r developed oth r valvular l si ns.

With the advent of heart thete ization new po sibilitie f demonstration of the signifi anc of mitral regurgitati n became vailabl (table II 2) L g 15f and Werkö (1949) thus demonstrated the characteristic v wave in th pulm nary wedge tracing Direct d monstration of mitral regurgitation w made possible by left v ntricular angiocardiography using direct v ntricular puncture (Smith et al. 1956) but first becam a routine method when the method f Seldinge (1953) w u ed f th ter introduction in combination with trograde c theteriz ti n of the left v ntricl (Prioton et al 1957 Amplatz et al 1961) Contributing to th renewed inter st in mitral regurgitation w e th fact that losed mitral valvul tomy becam a routine method in the l t 1940s (Hark n et al. 1948 Bailey 1949) and that mitral regurgitation wa an occasional unexpected finding at operation. The inte st in mitral egurgitation wa d monstrated by Brigd n and Leatham (1953) art cl reviewing 30 case with mitral egurgit tion as th only cardiov cular abnormality M tral insuff i ncy w s firmly established as dise se ntity when symposium in th lat 1950 was h ld on the subject of mitral regu gitation alone (Symposium on Mitral Regurgitation 1958) It thu be came m mportant t find method f eval ting the degree of m tral regurgi tation (hapt III) and d scribing th ha modynami d sturbanc cau ed by mitral regurgitation (chapt IV)

The r newed int est mitral insufficiency also resulted in th ediscov ry f oth type of mit al regurgit ti n than that of cuspidal origin, thus Askey (1950) nd Sand et al (1957) d cribed ruptu f papillary m scl and Os- mundson et al (1958) Shapiro (1959) O mundson t al (1961) and Menge et al. (1964) review d s of rupture of the chorda tendin e F rthermore new syndrom were d scribed Papillary M scle Dy function (Burch P squale and Phill p 1963) and the Bill w ng C sp Syndrom (Barlow et al. 1963 Segal and Likoff 1964 Hancock and Cohen 1966 C il y et al 1966) (Charbodet had how ev alre dy in 1878 given largely unnoticed eport of a patient, in whom mitral insuff y w diagnosed clini ally t autopsy f broai of left v ntricular p pillary m scl w found, imilar cases h e been reported by B sco in 1935 and Hope and A stin in 1952 (Sande et al 1971))

Surgical treatment of m tral insuff i ncy w tt mpted by Harken et al. (1954) In th following year numbe f method for reconstructive surgery w introduced but f w were able to stand the test f tim A method f ope tion f ruptured hord e tendine e d scribed by McGoon (1960) however

is still used A major breakthrough was the introduction of an artificial valve prosthesis (Starr and Edwards 1960) Since then, insertion of a valve prosthesis has become a routine treatment of mitral regurgitation using a variety of prosthetic valves made of artificial materials as well as hetero- and homografts.

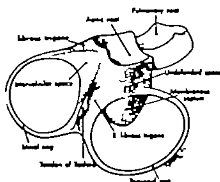
Chapter II

Anatomı and functıon of the mıtral valve normal and pathologıcal

In rd r to descrıbe mıtral insufficiency a short evıew of th normal anatomy and physiology of the mitral valve is felt t b useful.

ANATOMY

Th mitral valve apparatus r mplex co sists of th mitral leaflets (cuspid s) the chorda t ndinea the papillary muscl and the l ft ventricular wall



F g II 1 Diagram f th fibrous k let of th heart (reproduced from du Pl si and Marchand. The anatomy of th mitral val and it associated structures (Thorax 1964 19: 221 by kind p rmi sion f the authors and th publ sh s)

Before describing the mitral cuspid s it i necessary t d scribe the supporting tissu f the leaflets the mitral ring (annulu mitrali) As seen from fig II, 1 the mitral annul i part of the fibrou keleton of the heart. The anteromedial third f th annul is rather solid structure intimately

attached to the aortic root, anteriorly the annulus is made up of the trigonum fibrosum sinistrum (left fibrous trigone) posteriorly by the trigonum fibrosum dextrum (right fibrous trigone) and between these two structures the annulus is formed by a broad membranous structure area intervalvularis (the intervalvular space) In the outer and lateral two thirds the annulus is a considerably thinner fibro-elastic structure (Chiechi et al 1956) described by du Ple sis and Marchand (1964) as a fibrous thickening of the base of the left ventricle As described earlier the mitral valve tissue is attached to the annulus the left ventricular and left atrial musculature is inserted into or takes its origin from the annulus. The deep bulbospiral muscle in particular encircles the mitral annulus (and aorta) (Robb and Robb 1942)

The mitral valve consists of a continuous veil (Harken et al. 1952) This veil has two maj r indentations the commissures These indentations divide the veil into two leaflets: cuspis anterior (aortic septal, major or antero medial leaflet) and cuspis posterior (ventricular mural minor or postero-medial leaflet) As described above the commissures are not devoid of valve tissue but the width of the valve tissue is le s here; a description of accessory mitral leaflets is thus not a necessity Whereas the anterior mitral leaflet usually does not show indentations Ranganathan et al (1970) described two minor indentations (clefts) in the posterior leaflet, thus dividing this leaflet into 3 scallops. Each leaflet consists of a peripheral rough zone (zona densa) and a membraneous zone (ona membranosa) closer to the annulus A distinct ridge (linea occlusionis) separate th two zones and is the meeting line of the two leaflets The roughness of the zona densa is in part due to the insertion of the chordae tendineae Ranganathan et al (1970) describe an additional zone in the posterior leaflet the zona basilaris located between the zona membranosa and the annulus here some chordae tendineae are inserted (chordae tendineae basilares) Microscopically the valves contain fibrosa (dense collagen bundles) spongiosa (loose collagen tissue) and muscle tissue (as a direct extension from the left atrial wall) the valves on the atrial and on the ventricular side are covered with endocardium (endothelial cells) (Montiel 1970 Fenoglio et al 1972) The muscle layer contains both vessels and nerves Chiechi et al (1956) found that the area of the anterior leaflet was greater than that of the posterior leaflet (for men an average of 651 mm^2 (range 427 633 mm^2) compared to an average of 384 mm^2 (range 270 532 mm^2) for women 563 mm^2 (413 714 mm^2) compared to 334 mm^2 (413 456 mm^2) The total mitral valve area was considerably greater than that of the annulus (rifice area) for men an average of 1306 mm^2 (rang 1000 1770 mm^2) compared to an average of 793 mm^2 (range 672 1021 mm^2) for women 1220 mm^2 (970 1518 mm^2) compared to 642 mm^2 (490 875 mm^2)

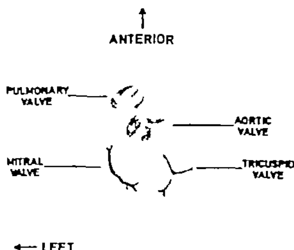
The chordae tendineae are cords of fibrous ti sue in the l ft ventricle extending from the tip of the papillary muscle or the left ventricular wall to the mitral valve leaflets Recently Lam et al (1970) have given a revised and detailed description of the different types of chordae tendinea Commissural chordae insert in a fanlike structure in the commissural area. Rough zone hordae ins rt in the zona dens of both leaflets usually dividing into 3 minor chordae before insertion; among the rough zone chordae two chordae are described as being particularly thick and strong (strut chordae) Basal chordae are the only chordae which do not originate from a papillary muscle but from the posterior v ntricular w ll They form singl strands and insert into the basal are of th posterio leaflet. Th chordae are relatively short and thin and flare out only just prior to insertion. Cleft hordae insert into the indentations of the posterio leaflet after having gr dually given off minor chordae Fal e chordae pas from papillary muscle to papillary muscle from p pillary muscle to ventricular wall and from ventricular wall to ventricular wall

The papillary muscles are two trunks of specialized trabeculae carneae connecting the mitral valv to the l ft ventricular wall by the chordae tendineae Each trunk originates from the junction of the middl and apical thirds of the l ft ventricular wall (v d. Spuy 1958) the antero-lat ral trunk coming from the antero lateral wall, the postero-medial from the posterior

wall close to the interventricular septum (Estes t al. 1966) The papillary muscl can b adherent to the ventricular wall (t thered) or freely projecting into the v ntricular c vity as a finger although intermediat forms are een (Raganathan and Burch 1969) Th antero lateral trunk f a papillary muscle usually onsists of one major head or belly (caput) although 2 or 3 head are seen in 17 p r cent of ases (Chiechi et al. 1956) On the oth r hand th postero-medial trunk usually has 2 3 o even 4 heads in 54 11 and 5 p r cent of cases espectively whe eas single head i less common (30 per cent of cas) (Chiechi t al 1956) Close to the tip the head of a papillary muscle may divid int minor heads (apituli) (Morrow et al 1968) Each trunk f papillary m scl suppli both mitral leaflets with chorda tendine Thu the antero-lateral papillary muscl supplie chord e to th halves of the two leaflets cl st to th antero l teral ommissure

Th arte ial supply to the p pillary muscles has recently been described by Raganathan and Burch (1969) The antero-lat al papillary muscle receiv s it supply from the descending o circumflex rami f th l ft coronary artery Th post ro-medial papillary muscle obtain art rial blood from th oronary artery branch, which i th dominant supplie of the post rior wall i e either th ircumfle amus of the left cor nary art ry or th right coronary artery P netrating branch s from these epicardial ronary arte ie reach th papillary muscles. If the papillary m scl is finger lik in shap a central art ry is the m in suppli r of art rial blood otherwise th blood supply com from more penetrating art ri s The papillary muscle are then supplied by th B type art i f Este t al. (1966) as is the for th endocardium Th innervati n t both papillary muscl m from the left bundle branch of His, the ant ri branch supplying the ante o-l t al papillary muscle th post rio b anch supplying the post ro-medial muscl (Lev 1964)

As een f om fig II 2 th line of cl sure between th mitral leaflet runs antero-l teral — post ro medial, the location of the two commissur ndi t s Th mitral orific (and the l ng axis f the left v ntricle) face mainly to th left but also nt ly and downward (Grant 1953 Silverman nd Hurst 1968) The papillary m scl hav th am directi n as th axis f the l ft v ntricl Although th rti and th mitral stia share a common opening in th left ventricl th y l t an angl of 40° t each other (du Pl and Marchand 1964) In ts open positi n, the anterior mitral val e i d viding line betwe th inflow and outflow area of the left ventricle.



F g II 2 D gram f th b of th h art see from above to d monstr t the orientati f th mitral val and it rel tion to th other heart val e

NORMAL FUNCTION OF THE MITRAL VALVE

Although it has long been appreciated that the function of the mitral valve is to allow for a flow of blood to pass from the left atrium to the left ventricle during diastole and to prevent any flow of blood from the left ventricle to the left atrium in systole the exact mechanism has been a matter of dispute for at least 60 years. Recent technical aids such as angiocardiography ultrasound cardiography and direct pre sure measurements in the heart chambers have helped in solving these problems

Using ultrasound technique Shah et al (1970) showed that following atrial contraction, closure of the mitral valve occurred both in sinus rhythm and in complete atrioventricular block. Brockman (1966) in animal experiments, showed that after the peak of the a wave in the left atrial pressure tracing had occurred a pressure gradient was established between the left ventricle and the left atrium. The mechanism of mitral valve closure during left atrial relaxation would appear to be explained as follows The left atrium acting as a booster pump dilates the left ventricle in late diastole by stretching the elastic elements in it. Following cessation of the left atrial pump pressure ("left atrial relaxation) the elastic elements in the left ventricle "contract thus causing a displacement of fluid towards the left atrium hereby closing the mitral valves. This theory is supported by the decrease in left ventricular diameter following left atrial relaxation, as illustrated by Brockman s fig 1

Left atrial contraction (and the following relaxation) is not the only way of closing the mitral valve Shah et al (1970) demonstrated in their ultrasound studies that also in the absence of atrial contraction (and relaxation) mitral valve closure will occur during left ventricular contraction. Brockman (1966) similarly described a small increa e in the left atrial pressure followed by a decrease (c wave) simultaneously with the early systolic increase in left ventricular pressure the a v valve closed by the rising intraventricular pressure much as a door is slammed shut by a sudden gust of wind.

Besides the above mentioned mechanisms for closure of the mitral valve a breaking jet effect has been postul ted (Henderson and Johnson 1912)

The function of the papillary muscles and their tendons (chordae tendinae) is generally agreed to be that of restraining the movements of the mitral valv es in systole This function ha been proven clinically as massive mitral regurgitation results when rupture of the body of one papillary muscle occurs (Brock 1950) Less evid nce is available for the importance of active con traction of the papillary muscles. On the contrary it has been proven in animal experiments that solated m assive infarction of the whole body of one papillary muscle does not result in mitral insufficiency (Mittal et al 1971 Tsakiris et l 1973) The role of papillary muscle contraction in losing the mitral valve is not yet clearly established but possibly contrac tion of the papillary muscles important in preventing mitral regurgitation during normal strain and in pathological situations; for example combined infarction of a papillary muscle and the surrounding area of the left ventricu lar wall will result in mitral regurgitation, whereas regurgitation will not occu in the case of isolated infarction of the same are of the left ventricular wall (Mittal et al 1971 Tsakiris et al 1973)

An additional mechanism fo closing the mitral valv s ha been d scribed n th studie by Davis et al (1963) By placing l ad marker n the mitral nnulus in animals and l ter examining the movements of the markers as se n on cinefilm taken during roentgen exposure the m tral ostium was shown to narrow by 24 54 per cent of t dilated area The deep bulbospiral muscle of Robb and Robb (1942) could conceivably cause this contraction. As the mitral valv area i normally larger than the mitral ostium annular contraction not likely t b of importance during normal cond tions but m ght be f importance during pathological conditions, and thus represents an additional safety mechanism.

Recently well defined bundles of striated muscle hav been found in the mitral valves in animals and man (Cooper et al. 1966 Montiel 1970) Th se

muscles appear to represent a continuation of the atrial musculature The function of this valvular musculature ha been assumed to be that of aiding in closing the mitral valve and p eventing ballooning This ha not been proven and it has not been examined wh ther these supposed mechanisms are of significance in th function of the mitral valv apparatus.

There ha b n l discussion and fewer investigation on the opening f the mitral valve The mitral valv opens wh n th rapidly declining ven tricular p sure fall below atrial pre sure (Brockman 1966)

MITRAL REGURGITATION THE PATHOGENIC MECHANISM WITH SPECIAL REFERENCE TO PATHOANATOMY

In this secti n review will be given of th patho anatomi al and etiol gical mechanism (table II 1) In p eparing thi review th following uthor have been of great help Levy and Edwards (1962) Souli et al. (1962) Marton (1966) Burch et al. (1968) Silverman and Hurst (1968) Sander t al. (1971) Perloff and R berts (1972)

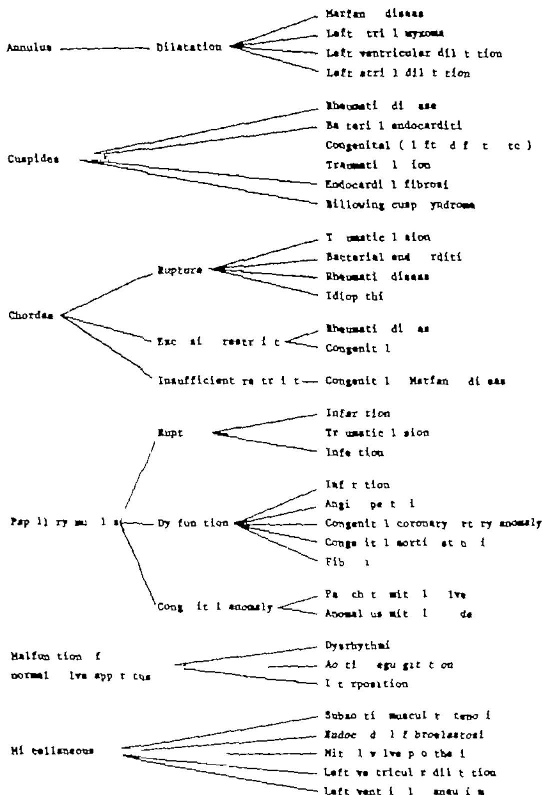
ANNULAR DILATATION

It is logical to ssume that dilat ti n of th mitral annul by pulling th leaflets fr m each othe could se mitral regurgitation. As d scribed arli the mitral valv area is consid ably greater than the mitral stium, accordingly the must be significant enlargement before mitral regurgitation an occur Eval ati n of this mechanism howev i made difficult by th fact that annular dil tation is often noti ed when other po sibl mechanism for mitral regurgit ti have b en operating

In Marfan dise severe mitral regu gitation might occur without abn rm l ti of l aflet o subvalvular structure a larg dil tation of the mitral ring has been described in thi dis se (in th se eported by Dietzman et al. (1967) a diam t of 8 cm was d scribed) In the cas f MacVaugh and Joyner (1971) a l ft trial myxom w regarded th of th annular dil tation. When th left ventricle enlarged as in congestive heart failur a murmur typical of mitral insuffic ency is oft n h ard t th pex. It has be n customary t assume that l ft v ntricular dilat ti n sed dil t tion of the mitral ring and thu mitral gurgit ti n (Edwards 1958) but oth mechanism ould also be ssumed to operate in th ircumstanc (e l t) H nani et al (1972) showed that nnul dil tation w s common finding at autopsy in e of non bstructi e ardi myop thy but mitral egurgit tion, evaluated at autopsy by a wat r test, ould not be rel ted to the degree of annular dil tation.

Wh n dil tati f th mitral ring occur nly the outer two-thirds can take part in thi the ant ro-medial o e third i anchored to th aortic root. Levy and Edw rd (1962) think that l ft trial nl rg m nt in itself might cause poste

Table II 1 Pathogenesis of mitral regurgitation.



rior and downward displacement of the outer part of th mitral ring to which th post rior mitral leafl t is attached and thus r sult in mitral regurgitation.

Perloff and Roberts (1972) postul te that th dil tatio of the l ft ventricle will c use insuffi ient ontraction f th previously d scribed annular ontracti n in systole, and that this alon or in combination with oth r fact r will c use mitral insufficiency

Silverman and Hurst (1968) sume that calcifi ation of the mitral ring as een for exampl in eld ly people an se mitral regurgit ti n by preventing systolic annular ontr ction. It i difficult to accept this theory knowing that t autopsy leaflet are normally will exceed that of the mitral rifice by safe margin, a d scribed earli r

CUSPIDAL DEFICIENCY

Th most c mmon c u e of mitral regurgit tion is probably rheum ti cuspidal deficiency The link between group A streptococcal infection nd rheumati heart dise se which ha been recognized clim ally for a long time (B khaug 1927) has recently been supported by the finding f immunologi al cro reaction be tween group A streptococ al polysa charid and glycoproteins of heart valv (Goldstein et al. 1967) Burch et al (1970) have sugg sted recently that viruses pl y an ctive rol in th production of rheumatic heart disease The cuspidal change produced by rheum tic fev hav be n described by Rusted et al. (1956) in two types In the first type dherenc f th leaflets occurs at the edges, thus narrowing th orifi Rusted et al (1956) thought that the adh rence started at the commissur but Brock (1952) denied thi and d scribed th adh renc as taking pl ce at critical ar as of th l aflet edg pproxim tely 1/3 f th distance from th annulu A the adh renc progress th l afl ts bec me f sed leav ing finally only a small entral opening In thi type of rheum tic affection, mino mitral nsuff ncy m y occur du to decre sed mov ment f the mitral l aflet (Brock 1952) Th second type of rheumati cuspidal affection c use d f rmation by rend ring th leaflet thi k, stiff and le thery Late th cusp do shrink and are calcified. When shr nking and retraction occu s part of the oc rring proces gurgitation will esult. This regurgitation an be severe but sually companied by some d gree f stenosi Seltzer et al. (1972) thought that th deform tion type f mitral rheumatic disease was mainly sed by an bnormal fl w patt rn initi ted by cuspidal adh enc and minor spidal d f m tion. Th m tral val e i th most c mmon site of rheumati valvular ffection. Lepeschkin (1952) proved by simple mathem tic that this was du t the m tral valve having to ndur the high st ounter-pre sure among th cardi alv s.

B ct rial ndoc rditi s noth r common au e f cuspidal mitral regurgita tion. Bacterial ndocarditi can p oduce egurgitation by creating perfor tions

through the valve substance with or usually without prior rupture of a mycotic aneurism (MacLean and MacDonald 1957 Edwards and Burchell 1958) Another type of lesion is erosion and destruction of the leaflet edges (Edwards and Burchell 1958 Soulie et al 1962) A less common form of lesion is fusion of the posterior leaflet to the posterior wall of the left ventri le with resulting regurgitation (Becker et al 1951) This lesion is due to organisation of vegetations which are deposited in the angle between the posterior leaflet and the left ventricular wall (Levy and Edwards 1962)

Endocarditis most often occurs in valves which are diseased prior to infection. Th percentage of this varies from 85 to 60 (Robinson and Ruedy 1962 Wilson 1963) Infection of the mitral valve from a neighbouring focus has b en reported to occur in aortic valvular steno sis (Edwards 1972) and subaortic muscular stenosis (Vecht and Oakley 1968); usually only the anterior mitral dusp is infected in this way

A number of ba teria have been described as capable of producing endocarditis; previously non-haemolytic streptococci were the most common cause but staphy lococcal nfection is now probably ev n more important (Robertson and Ruedy 1962 Wilson 1963) Endocarditis is now not only caused by bact ria but also by fungi (Finland 1972) The r sulting mitral regurgitation can be severe demand ing surgery within a short interval

Among the ongenital causes of m tral insufficiency of cuspidal location, cleft mitral leaflet the most common. This defect is part of the endocardial cushion d fect anomaly and thus usually associated with an atr al septal defect although this s not nec sarily th case (Creech et al 1962) The resulting m tral insufficiency gen rally of minor importance as accessory chordae are present close to the cleft (Levy and Edwards 1962) but marked mitral insuffici ncy may be present if there is major defic ency of cuspidal tissue Similar to an isolated cuspidal cleft, an solated defect of valvular tissue not reaching the edg ha be n reported (Levy and Edward 1962)

Rarer causes of ongenital uspidal insufficiency are seen a a left sided Ep stein anomaly in corrected transposition (Malers et al 1960 Schibl r et al 1961) A similar Epste n lik anomaly ha be n reported in cas which appar nt ly had b cuspid mitral valve (Actis and Milocco 1966)

In th Hurler syndrome and in Ehl r Danl d sease mitral nsufficiency has been d scr bed as a rare occurrence due to small nodul and thickening and scarring of th mitral valve and chordae (Madison et al 1963 Krovetz et al 1965) As these report depend n single cases it difficult to se whether the cardiac disea e s a c nsequenc of the gen ral disease or represent patients suffering from two typ f dise s These remarks also apply to the report of mitral in sufficiency occurring in a c of osteogenesis imperfecta (Heckman and Stein berg 1968)

Traumatic cusp l si n causing mitral insuffic ency are relatively rar The most common probably surgi al, as a compl cation to mitral valvulotomy

(Frater 1967) Direct and indirect trauma f mitral valv l aflets has oth rwise rarely been documented t autopsy o ope ation. Adam (1927) reported a ase where a pistol bullet produced a hole in th anterior mitral cusp M Laughlin et al. (1964) eported case of avulsion of a mitral cusp from the annulu following an automobile accident. In anoth r cas of car ac ident Goggin et al. (1970) de scribed splitting of th posterior mitral cusp

Endomyocardial fibrosis is disease mainly occurring in East Africa. The finding i fibrosis of th endocardium and adjoining myocardium of the left and right ventricl (D vies and Ball 1955) The fibrosi often ontinu from the papillary muscle to the chord and further t th cuspid Thi proc ss mainly affect the post ri cusp which is tethe ed down t the left ventricular wall by adhesions and fibrosis. This leaflet i thu immobilized and mitral egurgitation results (Davi and Ball 1955 Fowl r and Somer 1968) Thi lesion is similar to that d scribed above in bacterial endocarditis

Th billowing cusp syndrom i haracterized linically in th typical ase by late systolic apical murmur a mid systolic cli k o honk and electrocardi graphically by low or inv rted T w ves in II III and aVF leads prolonged Q T interval and prominent U wav (Bitt and Sosa 1968) Angiocardi graphy (p e ferably ineangiocardi graphy) shows prolapse of the post ri leaflet into th l ft atrium (Cril y et al. 1966 Trent t al. 1970) Micro copy of xcised val es has rev aled myxomatou chang (Bitter and Sosa 1968) similar to those seen in Marfan syndrom (Grossman et al 1968) Read et al (1965) onsidered the anomaly f rm fruste f the Marfan syndrom and regarded th increased pli bility of the valv the sential part of th synd me which they called the *floppy valve syndrom*

As thi syndrome occurs in familie (Sh ll et al 1969 H nt and Sloman 1969) t i lik ly that ongenital onnectiv ti su d fect xists in these val The p tients are sually symptom ti but th mitral insuff ci ncy might progre s t a signif ant degree Anoth symptom i angina pect ris which as well a the electroc rdi gr phi change is thought to be due to the prol psing (usually po teri) leaflet omp ssing th left ircumflex o onary artery (Barlow et al. 1968) *It be mentioned that sudd n death does occur in thi disea* Pomeranc (1969) ha described myxo d changes of th mitral valve in l per cent of autopsi and regarded thi non specific hang resulting from many tiological pro- The occurrenc of th syndrome arly in lif in some families howev would suggest that ongenital f ct r doe pl y a signifi ant ole

DISEASES OF THE CHORDAE TENDINEAE

R pture of the hord t ndin now w ll rec gnized clinical entity due to the typical finding (ee l t) and to th po sibility f cure th ough surgical in t rv nti n (al repl cement reconstructi operation)

Traumatic rupture is probably n t common. Only few cases have been reported caused by indirect trauma. In the case already quoted f om McLaughlin et al. (1964) rupture of the chordae occurred as well a avulsi n of the anterior cusp Manhas et al. (1971) described a case of isolated chordae rupture due to a fall from a horse Direct trauma causing rupture can take place during closed mitral valvulotomy (Marchand et al 1966) In these circumstances the resulting regurgi tation is probably minor a a l aflet which is subjected to valvulotomy usually doe not move freely

Among the non traumati causes the most c mmon is probably endocarditis, either in the acute state o later as a consequence of the resulting weakness (Osmundson et al. 1961) Next to endocarditi rheum tic fever is generally re garded as a common aus (Manhas et al 1971) although the expe enced patholo gist Edwards (1971) doe not ac ept thi Structural weakness a seen in Marfan syndrome i described as a ignificant etiological factor (Edwards 1971) Athero ma with necrosi and calcificati n wa described by Marchand et al. (1966) in a c e of ruptured chordae t ndineae Rupture of appar ntly normal chordae tendin ae is not uncommonly eported (Frothingham and Ha s 1934 January t al 1962 Manha et al 1971) In these ases of idiopathic rupture Marchand et al. (1966) speculated that increased strain on the chorda as seen in enlargem nt of the l ft ventricl w a contributing f ctor When ruptur of a chorda t ndine occurs the corresponding unsupported flail segment of the leaflet rise a a hood, beyond th gene al level of the supported part f the leaflet' (Edwards 1971) This def rmity directs th blood str am in the direction opposit to th t of the hood The blood str am can be recogniz d by the resulting jet lesion in the left atrium (Edw rds and Burchell 1958) It s obvious that the d gree of mitral gurgitati n thus produced will dep nd on th location and numbe of the ruptured chordae

Mitral regurgitati n d e to cho dal dise s without rupture can occur in two type of situ tion. Undu r straint f the mitral v lv by abn rmal chord e is most commonly seen in rheumatic h art diseas Th ch rda re sh rtened and/ r thickened. In the later state f s on of the chord usually occ s which in a sociation w th the deformed cuspides ses th m t al valve to b converted to a funnel shaped structure (Rusted et al 1956) As ongenital heart dise se shortened ch rd an be seen in associ tion with c rrected transposition (Talne t al. 1961) but hav also b n d cribed in Ehl Danlos disea e (Madison et al. 1963) Abnormally inserted chordae have been d scribed n mm n atrio ventricular canal but apparently prevent ce sive movem nt of th split ant rior m tral leaflet. If the cleft s sutured th s access ry chord e may c se undue restraint n the nt o cusp nd thus regurgitation (Edwards 1960) Chorda of abnormal origin an also ca se mitral egurgitati n (Levy and Edward 1962) Insuff cient chordal restraint on th mov ment of th m tral leafl t i seen in Marfan dise se where abnormally l ng and thin horda hav be n de scribed (Raghib et al 1965 D etzman et al 1967) In the pre iously described

billowing cusp syndrome *Bittar and So (1968) regarded elongati n of the chordae tendinea as a significant factor*

PAPILLARY MUSCLE DISEASE

Ruptur of papillary muscl e rar disease The degr e of the resulting re gurgitati n dep nd on the extent of th l si n (Roberts and Cohen 1972) Rupture of an entire trunk is followed by severe mitral egurgitation (Austen et al. 1965 Torre t al. 1967) often sulting in early death (Askey 1950) If one head (caput) or an apical head (capitulum) ruptur r gurgitation also result th d gre de p nding on the number and insertion of th detached horda A ase in which the horda ar detached from the ape of papillary m scl probably represents an extrem f papillary muscle rupture Th most common cause of rupture i myocardial infarction (Sande et al. 1957) but the incidence f rupture of a papillary muscl among c se of myocardial infarction i low 0 3 1 0 pe ent (Cederquist and Söd rström 1964) Rarer auses f rupture are seen in inflamma t ry di es Myocardial absc (Hackel 1953) syphiliti necro i (Spalding and Glahn 1921) periarteritis nodosa (A sten et al. 1965) and bact rial endocarditi (M rat 1804)

Traum tic ruptu h s been reported in mitral valvulotomy (Brock 1950) but i pparently not unusual in severe traumati ccidents Parmley et al (1958) among 546 utopsy ses of tra mati heart injury reported 23 ses wh re papillary m scle rupture occurred a well ardiac rupture (th se autho did not specify whether th ruptured papillary muscl belonged t th l ft or right v ntricl)

Four other ca of tr m ti papillary m scl rupture have bee reported, all fatal within short p riod of time (Gl ndy and Whit 1936 P yne and Hardy 1937 M L ghli t al 1964 Gomez and J ckson 1966) I all case the severe tr um w s th result f an automobil ac d t, but ne se occurred in a boy wh fell from swing and hit his h st n stump (Gomez and J kson 1966)

DISEASE OF PAPILLARY MUSCLE AND ADJACENT LEFT VENTRICULAR WALL WITHOUT RUPTURE

In 1963 Phillip Burch and P squal described th syndrome of papillary muscle dysfunction i. th bserv ti n th t dise se of l ft v ntricular papillary muscl ould ca m tral r gurgit tion. A p eviously d scribed, experim nts hav stablished th t a l sion of th papillary muscl has to be ombined with l sion of th adjacent left v ntricul r wall in rd to produce mitral regurgitation (M ttal et al 1971) As a onsequ nce of thi th term papillary muscl dysfunc ti n will in th p ent study be sed to d scribe mitral regurgit tion produced by

a combined lesion of a papillary muscle of normal shape and its adjacent left ventricular wall

Clinically the most common cause of papillary muscle dysfunction is ischaemia. Heikila (1967) described an apical systolic murmur typical of mitral insufficiency in 107 out of 195 patients suffering from myocardial infarction. Eighteen patients with a systolic murmur came to autopsy and seventeen were found to have major papillary muscle infarction, in contrast the ten patients without a systolic murmur who also came to autopsy did not have any significant papillary muscle disease Cheng (1969) diagnosed papillary muscle dysfunction in eighty patients using clinical criteria. Twenty four of these patients had cine ventriculography performed; in all of these patients mild to moderate mitral regurgitation was demonstrated. In twenty patients coronary cinearteriography was performed Significant obstruction of one or more major coronary arteries was demonstrated in all but one in 50 per cent all major coronary arteries were severely affected by atheromatosis Shelbourne et al (1969) similarly found three vessel coronary artery disease in all of fourteen patients suffering from papillary muscle disease and abnormal l ft ventricular contracti n in all but one of these patients Brody and Criley (1970) described intermittent papillary muscle dy function in a patient who developed a systolic apical murmur simultaneously with angina pectoris; the murmur as well as the pain dis ppeared following sublingual application of isorbid dinitrate Ischaemic papillary muscle dysfunction can be so severe as to warrant surgery M tral valve replacement with significant improvement has been reported in a few patients (Fluck et al. 1966 Spencer et al 1967)

Congenital papillary muscle dysfunction has been described by N ren et l (1964) An apical pansystoli murmur was found in six out of nine patients with an anomalous origin of the l ft coronary artery from the pulmonary trunk. In the only two patients in whom left ventricular cineangiograms were made mitral regurgitation was demonstrated. E ch of the four pat ents who died and had necropsy performed showed inf rction of the posterior papillary muscl in two cases the anterior p pillary muscl was also infarcted. Moller et al (1966) described papillary muscle nfarction in all of eleven ases of congenital aortic stenosis In fiv patients who had left ventriculography performed mitral regurgitation was demonstrated Mitral insuff c ncy f llowing a blunt trauma w s demonstrated by ventriculography n a young patient. Autopsy showed isolated p pillary muscle infarction (Schroeder et al 1972)

Among other causes of papill ry muscle dysfunction, Marcus et al (1969) described solated fibroma of a p pillary muscle and the underlying part of th left ventricle in a single case Th coronary arteri were normal

Congenital abnormal ty of th p pill ry muscl au ing mitral regurgit tion has only recently been d scribed. Shone et al. (1963) descr bed the parachute mitral va " in which the chordae te from a single p pillary muscle Th haem nsequence is mi gitation, often combined with sten si

(Glancy et al. 1971) This abnormality ha so far not been reported as an isolated defect, but is usually sociated with supravalvular mitral ring, subvalvular muscular stenosis and coarctation of the orta (Shon et al. 1963) although a number of other abnormalities have been reported (Glancy et al. 1971) The clinical pictur is in consequence oft n dominated by the associated anomaly

In 1967 Layman and Edward described Anomalou Mitral Arcade In this ongenital disease a bridge of fibrou tissue connect the two papillary muscles n each sid with the lowe edge of the anterior mitral l aflet in the middle Th chordae of th anterior mitral l aflet are short or ab ent; th papillary muscles are thus in almost direct continuity with the anteri mitral leaflet. From the pathologi al finding and th presenc of a systoli murmur the haemodynamic nsequenc of this abnormality is thought to be mitral regurgitation. Castaneda t al. (1963) however late d scribed case in which sev re mitral stenosis wa present.

MALFUNCTION OF THE NORMAL VALVE APPARATUS

This type of mitral insufficiency is only onsid red t be present if any anatomi al abnormality of the mitral pparatu i absent.

Dysrythmi ar generally nsidered au e of mitral regurgitation. Clini ally extrasystol have been ob rved to cause mitral regurgitation during left ventriculography (Honey et al 1969) experim ntal egurgitati n has been onfirmed to occur when extrasystol occurred in mid cycl (V and nberg et al 1969) In ca of t tal trioventricul block, trial ontra tion not followed by ventricular contraction will ca regu gitation (William et al 1968) In d g e periments trial fibrillati n was shown to caus mitral egurgitation (Daley et al. 1955) but n trial fibrillati n in man, mitral r gurgit tion is not always seen as d scribed by Braunwald t al (1966)

M tral gurgit ti has b n seen in rtic regurgitation, probably due to l te diastolic reve al of the ventricular atrial grad ent (Lochaya et al 1967)

Mitral gurgitation due to interpositi n between th val is se n in left trial myx ma (Penny et al 1967) A similar ffect an be expected from c the t tr velling through the mitral ostium (Lansing et al. 1966) Th apical systoli murmur oft n h ard in acut heumati feve and ndocarditis (Friedberg 1956) probably due to int rpositi n of veg tations.

MISCELLANEOUS TYPES OF MITRAL REGURGITATION

In att mpt t syst m ti description of an spect f a dise se th author often nds up with som *dise ses which d not quite fit int hi* system. Thi i *also* th ase in the pre nt review where und th h ading of miscellaneous type

of regurgitation will be listed in which the pathological mechanism is not well defin ed or agreed upon; other reasons for inclusion under this heading are small num ber of cases or that the disease could be listed under more than one of the pre vious main groups.

Mitral regurgitation has been demonstrated in a majority of the case of sub-aortic muscular stenosis (40 100 per cent) either by dye dilution studi s or by angiocardiography (Cohen et al. 1964 Wigle et al 1969) The regurgitation oc curs from the high pressure area of the left ventricle to the left atrium (Dinsmore t al. 1966) The sequence of happening described in systole eject obstruct leak, illustrates well that regurgitation occurs late in systole (Dinsmore et al 1966) Regurgitation is abolished or reduced if surgical amelioration of the obstruction has been successful (Wigle et al. 1969) Similarly a pharmacologically increas ed pressure gradient across the outflow tract will increase the regurgitation; de crease of th gradi nt by oth r drugs will decrease the regurgitation (Wigle et al. 1969) Autopsy h s shown normal mitral valves in the majority of cases but Fix et al. (1964) eported four cas with thickening of the valves or hord e The mechanism of regurgitati n has not been finally established but a numbe of theories hav been advanced. D st rtion of the anterior mitral leaflet by the hyper trophied muscl (Cohen et al. 1964) displac ment of the attachment f th mitral valve by the hypertrophied muscl (Cohen et al. 1964) abn rmally aligned papil lary muscl in a small left v ntricular cavity in late systole (Criley et al 1965) encroa hment of hypertrophied muscle on the chord e (Dinsm re et al 1966) ab normal traction on th mitral leaflets by enhanced papillary muscle contraction (Dinsmore et al. 1966)

The observed mitral regurgitation described as varying from mild to severe (Wigle et al. 1969)

A whitish thi kening of the endocardium occurs in endocardial fibro lastosis. An apical systolic murmur often heard in thi disease This is g nerally re garded as being due to dilat tion of th left ventricle (Buchem et al. 1959) or to involv ment of the mitral valve in the disease proces (Lambert et al. 1953) Moll et al. (1964) however think th t fib oelast si is caused by other ardia anomalities They regard the primary ndocardial fibroelastosis as being due to mitral insufficiency which is caused by an bnormally high origin of th papillary muscle from the l ft ventricular wall

Mitral regurgitation following inserti of a prosthesis in the mitral stium can b due to paravalvular l ak or to malfunction of the nserted prosth sis. The f rmer usually oc ur in th immediate postoperative per od, but may pro gre later (Sander et al 1971) The regurgitation may be localized or mor diffu e and ircumferential (Kastor et al. 1968 Sander et al 1971) Calcifica tion of th annulus thought to be a c ntributory factor by severing th sutures (Danielson et al. 1967) Malfuncti n of th prosthesis can ause m ssive regurgi tation if th disc s locked into a fixed position (Low and Lefevre 1967 Saaman 1969 Vogel et al. 1969) Wear of the disc ball variance and hinging of disc

prosthesis hav all been reported t use malfuncti n nd regurgitati n (Edgett et al. 1967 Vogel et al 1967 Carey and Hugh s 1968 Vlasko and Leighton 1968 Conolly et al. 1970) The probl m of malfunction of prosthetic valve h recently been reviewed by Hyl n (1972)

For a long time it has been a clini al experienc th t systolic murmur simi lar to that of mitral insuff ciency was heard in sev re cardiac failur and th t it ould disapp ar on medical treatment (Friedberg 1956) Thi mitral regu gitati n in l ft ventricular dilatation has rec ntly be n a subject for discussion as to it pathogenesi A d sc ibed earlier in thi chapter th regurgitation has been ascribed to annular dilatation o to absent o insuffic nt annular contraction in systole During the past 20 years the subvalvular omponent of the mitral com plex have attracted considerabl interest and inv stigation, and alternativ ex planation for mitral insufficiency in this situati n have been advanced. If the left v ntricular apex migrat downward in a verti al directi n due t left ventri cular dilatati n, th chord and th p pillary muscles re assumed to be rela tively too short to ensur suff ent cl sure of the mitral l aflet (Levy and Ed wards 1962) If th l ft ventricl i nlarged mainly lat ally th direction of th pull of th papillary muscle( ) i changed from a more or less v rtical one toward horizontal directio (Edward and Burchell 1958) This m y result in l f effi ncy r straining the leaflet thu allowing th leaflet to ov shoot on nother hereby creating regurgit tion (Levy and Edward 1962) A mitral insufficiency in tself re te dil t tion of th left v tricl a vicious rcl m ght b expected xpre sed by Edward and Burch ll (1958): mitral insufficiency beg t mitral insuffici ncy Th subvalvular explanation f mitral *egurgit tion in left v ntr cular dil t t on b* been advocated by Burch *et al* (1968) particularly in th context of p pillary m scl dysfunction It should be noted that onc ntri left ventr cular hypertrophy th normal direction f th papillary m scle and chord pre erved (Est t al 1966)

Left v nt ula neur m an use mitral nsuffici ncy by 3 mechani ms s described by Ch ng (1969) If papill ry m scle included in th are f aneu m mitral insuff ncy is caused by th am mechanism as d scribed in this chapte und papillary m scl dy function, sensu stricti ne Displ m nt f th base of p pillary m scle ccompanying aneu sm f rm tion m y caus a hang in th directional axi f th papillary muscl and hord and thus re gurgitati n, described th chapte in the c f left v ntricular dil tation and mitral gurgitation. Finally the systol xpansi n of a tru aneuri m whi h incl d th b se of papillary muscl will prev nt ffi ient closure f th cuspide p ovided th systol outward displac m nt f the wall f the aneur sm s suff iently large s the papillary m scl and chorda t ndine in q estion will then be rel tively too short

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The observed mitral regurgitation is described as varying from mild to severe (Wigle et al. 1969)

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Mitral regurgitation following insert on of a prosthesis in th mitral ostium can be due to paravalvular leaks or to malfunction of the ins rted prosthesis. The former usually occur in th immediate postoperative period but may progress later (Sanders et al 19 1) The regurgitation may be localized or more diffuse and circumfe ential (Kastor et al. 1968 Sanders et al. 1971) Calcification of the annulus is thought to be a contributory factor by severing the sutures (Danielson et al. 1967) Malfunction of th prosthesis can cause massive regurgitation if the disc locked into a fixed position (Low and Lefevre 196 Saaman 1969 Vogel et al 1969) W ar of the disc ball variance and hinging of a disc

valuabl in differentiation *between mitral stenosi and regurgitation* (Benchimol et al. 1960) Ultrasoundcardiography has also been used in evaluation of mitral regurgitation; this m thod will be disc ssed in chapter VII

ANALYSIS OF THE LEFT ATRIAL PRESSURE CURVE

When heart catheterization became routine method in the late 1940 a high v w v in the pulmonary wedg pressure tracing was noticed in c se of mitral regurgitation (Lagerlöf and W k8 1949) The height of thi v wav (directly or corrected by oth r pre sure variables) measured in th direct indi ect pressure curv from the left atrium has sinc been used by some autho as an index of mitral egurgitation (Gorlin et al. 1952 Wade et al. 1952) However a normal height of the v wave despit th p esence of severe mitral regurgitation was described by Braunwald and Av (1963) Due to difficulti in correlating the height of the v wav with mitral regurgitation, Owen and Wood (1955) tried to correlate *mitral regurgitation t the shape of the descent of the v w ve (the y-descent)* through their Ry/v ratio Bentiv glio et al. (1961) howev questioned the value of the Ry/v ratio (and similar f rmulas f r d scribing the y-descent) in indicating mitral regurgitation. In the next chapt th value f the analysis of the v wave in the diagnosis f mitral egurgitation will b examined and discu sed; at this point it should b noted that analysi of th v wav would t most d scribe the haemodynamic r sult of mitral regu gitation, but not provide a measurement of the regurgitation itself

SEMIQUANTITATIVE ANGIOCARDIOGRAPHY

Angiocardiography using selective inje ti n f contrast medium into the left ventricle probably th m st commonly sed techniq for eval ation of mitral regurgitation t th present tim The cathet s usually passed into the left ven t cl from the aorta, cineangiocardi graphy i g ne ally the preferred technique Quantitati n i obtained by the u of grad Including quantit ti e eval tion the degree of opa f ti f the left atrium 1964) nd pulmonary veins (H ney et al 1969) th width and density of gurgitant jet (Hon y et al 1969) th time course of opacification of the trium and th rt (Mahl 1964) and eval tio f contrast tr um s compared t th t of the orta and th l ft ventricle. pl y 4 5 grades th l w st indic ting no egurgitation and gurgitation. Th intermedi t grad s are subjective

F w tt mpt at an evaluation of thi m thod hav been (1964) in his thorough review m ntioned th difficulti and pre su and h art rhythm sed by th catheterization graphy' well technical problems in about 40% of the

graphic assessment of the degree of MI was judged to be impossible or uncertain" Honey et al (1969) evaluated regurgitation using 4 grades indicating a variation in regurgitation from nil to severe All the cineangiocardiograms were examined separately by three observers. Each observer agreed with one of his colleagues in two thirds of the cases, but all observers agreed in only half" One observer evaluated the regurgitation twice and allocated the same grade each time in 83 per cent of the cases. Porstmann et al (1965) compared cineangiocardiographic evaluation using 4 grades with determination of regurgitation using a dye dilution technique (injecting dye into the left ventricle and sampling from the left atrium and the femoral artery) The patients were also divided into four groups according to the severity of mitral regurgitation as determined by the dye technique As to the presence or absence of mitral regurgitation, full agreement was reported A good agreement between evaluation of major and minor regurgitation was also reported whereas the division between grades 2 and 3 was more difficult. Unfortunately the variation in regurgitant flow (as determined by dye dilution) was not reported for each cineangiocardiographic group of patients. From these studies it appears that cineangiocardiography is a good method for proving or excluding the presence of mitral regurgitation, whereas the grading of m tral regurgitation by this technique is more difficult.

QUANTITATIVE DETERMINATION BY ANGIOCARDIOGRAPHY

Sandler et al (1963) and Arvidson and Karnell (1964) have described determination of m tral r gurgitation by comparing the stroke volume determined by angiocardiogr phy with the forward stroke volume determined by the direct Fick principl (or a suitable dye dilution method)

Determination of th size of the left ventricle can be accomplished using bi plane angioc rd ography on th s umption that the left ventricle has the shape of an ll psoid From the angiocardiographic frames the lengths of the three axes are calculated and corrected for magnification factor by th spatial vect r method" (Arvidson and Karnell 1964) or the longest measured length method" (Sandler et al 1963) The area length method (Dodge t al 1960) also assumes that the left ventricle s an ellipsoid but due to the often irregular shape of the left entr cl (LV) planimetry of the roentgenographic profile combined with determination of th length is used to determine the transverse axis Chapman et al (1958) d sc bed a method for det rmination of LV volume by the plani metrically determined rea f LV n the left ante or oblique and the right ante rior oblique projecti n. Det rmination of l ft ventricular vol me has also been described using only one projection a numb r of formulae have been described as reviewed by H rmann and Bartl (1968) one dimension being assumed or deduced from the other dimensions.

Determination of LV vol me by angiocardiography h s some built in errors

and difficulti The left ventricle rarely ha the exact shape of an ellipsoid, the volum f the papillary muscles and trabecul e carnea are incorporated in the measurement and the contour of th LV can be difficult to outline It is thu not surprising that av ag difference of 15 ml in volum det rminati n h ve been reported on omparing two method (Hermann and Bartle 1968)

In determinati n of stroke volume by angiocardiography the volume of th papillary muscl and possibly other f cto of importanc for volume determina tion are similar and thus f littl importance Gribbe (1960) Arvidson (1961) and Dodge et al. (1962) showed good correlation between determinati n f LV stroke volume by angiocardiography and the direct Fick method (r dye dilution techniqu) although som showed a significant disc epancy

When stroke volume det rmination by angiocardiography i used in ombination with det rmination f forward flow by th direct Fick (1870) method it should be possible to calculate the regurgitation flow F practical easons, however the two examinations cannot be performed simultaneously thu the cardiac output is not nece sarily the same during th two procedures; in th examinations by Ar vidson and Karnell (1964) the heart rate averaged 97 during angiocardiography compared to 80 during ardiac output det rmination (Fick) whi h would suggest that th f rward flows were not id ntical in th se two situations. Determination of strok volume i difficult in patients with ta hycardia marked arrhythmia (Sandler t al 1963) particularly so in patient with atrial fibrillation (Arvidson and Karnell 1964) Injection of ntr st into the l ft ventricl can itself cause ir regul h art hythm such as prematu be ts. Although these short ming have to be m ntioned t is most valuabl that a quantitative det rmination of th r gurgitati n an thu be btained. So far the exactn s of this m thod has not been ompared to oth quantitative m asur m nts but as practical guidanc Kennedy et al. (1970) stated that beca se of inherent inaccuraci in both the Fi k and angiocardiographic method 1 0 l/min. of calcul ted regurgitation w allowed for patients with pure mitral stenosis

SEMIQUANTITATIVE DETERMINATION BY DYE DILUTION CURVES

If dye is injected int a ntral vein or the ght h art a time concentratio curv an b obtained from an ar densitom t o a cuvette d nsitometer through which blood drawn from a syst mic art ry Th tim nc ntr ti n curve i wave-like: following tim int rval (ppearanc time) th e i a rap d i in concen tr tion to p ak. A sl wer fall (disappearanc slope) is seen next, followed by a ecircul tion wave I mitral egurgitati n the following chang ar een: di minished pe k, prolong ti n of th disappearanc slope and diminution o ab ence f recircul ti n peak (Wood and Woodward 1957) K rne and Shillingf rd (1955) described a decreased ppearanc time but thi w not noticed by Levinson et al. (1959) These findings f dilution curve dist rtion have been used in a numbe

of formulae for estimating mitral regurgitation, as reviewed by Nixon and Snow (1962) The changes described in the time concentration curve can also be produced by increased central blood volume (needle to needle volume) and are found when cardiac output is decreased (Hamilton et al. 1931 Korner and Shillingford 1956) Using a dye dilution curve one should accordingly be able to distinguish between slight and severe mitral regurgitation as the latter state would also tend to be accompanied by increased heart size and eventually decreased forward flow However the dye curve would be expected to provide a limited means to distinguish between patients suffering from significant mitral stenosis and significant mitral regurgitation, and this in fact has also been found (Resnekow 1961) Similar difficulties would be expected in evaluation of the degree of mitral regurgitation in patients in severe heart failure Polissar and Rappaport (1961) concluded a methodological study as follows: "As a consequence quantification of atrioventricular valve regurgitation through analysis of a single distal indicator dilution curve following proximal injection cannot be accomplished"

QUANTITATIVE DETERMINATION BY DYE DILUTION TECHNIQUE

Several authors have described the determination of mitral regurgitation by a single injection of a dye into the left ventricle followed by the recording of dye dilution curves from the left atrium and a systemic artery (Wood et al 1956 Woodward et al 1957 Milnor 1957 Sinclair et al 1960 Levinson et al. 1961 Gorelick et al 1962 Jose and Bernstein 1962 Günther 1966) The areas of the indicator dilution curves are calculated as for determination of cardiac output, and the regurgitant fraction of the left ventricular output can be determined as it is identical with the ratio between the area of the left atrial dilution curve and the area of the systemic artery curve In this method two factors are important: the mixing of dye in the left ventricle and appropriate sampling in the left atrium, as these problems are also present in the method described in this chapter they will be discussed later Levinson et al (1961) described poor reproducibility of the values obtained for the regurgitant fraction. The same group of investigators (Frank et al. 1967) later concluded that this vulnerable to error was due mainly to the presence of varying stroke volumes and insufficient mixing in the left ventricle which was particularly pronounced in the single injection technique They accordingly described a continuous indicator infusion technique the main change was that th dye was now injected continuously into the left ventricle in place of the previous bolus injecti n technique The regurgitant fraction was calculated as the ratio between the dye concentration in the left atrium and in the systemic artery the conc ntrations were determined t a time when equilibrium plateaus had been reached in the dy dilution curves following injecti n, but before the major rec rculation had occurred. This change in technique resulted in considerably improved correlation between repeated examinations The error of

estimate at the 95 per cent confidence limit however was still high (24 8 per cent) which was mainly ttributed to unrepresent tive ampling from the left atrium in the presence f incomplete mixing of indicator with blood" Another problem using th continuou dy infusion techniqu is wheth there is any re circul tion from the coronary artery circulati n (Rahimtol and Swan 1965) and th systemic circulation through the pulmonary circulati n t the left trium at the time f equilibrium plateau The difficulty in ttaining true plate u (a seen from fig 2 and 3 in the article f *Frank t al. 1967*) does suggest thi po sibility

QUANTITATIVE DETERMINATION BY CONTINUOUS INFUSION OF AN INERT GAS

The advantage of using an inert gas i place of a dye f r determination of mitral regurgitation by means of a continuou infusion technique is that the problem of ecirculation will be diminished, as th indicat r will be largely cleared by the lung provided th blood/gas partition oefficient i low The u e of a gaseous radioactive isotope provid s possibiliti s for easy determination. Lyngborg et al. (1965) described th se f the krypto isotope ^{85}Kr [1] f this purpose in a preli minary commum ati n; the principle and technique are d scribed bel w M roh et al. (1966 1967 and 1972) h ve d scribed th u e of ^{133}Xenon for determinati n of mitral regurgitati n. The princip in their m thod was that ^{133}Xenon in a sa lin sol ti n w infused int the left v ntricle. Blood wa simultaneously with drawn from th left tri m and sy temic artery and p ssed through glass c vettes in close proximity to scintill tion detect rs; th output of the e d tectors was both printed num rically and recorded n direct writing scillograph Th ecirculation t the pulmonary veins at 60 seconds following start of infusion w stimated t be an verage of nly 2 3 per ent of th art rial oncentration. On varying the pos ti n f the tip of the l ft atrial sampling catheter th chang in gurgitant fr ction w only 2 4 pe nt f th left ventricular output.

PRESENT INVESTIGATION

MATERIAL

77 pati nt we e elected for examination. They we e all admitted to medical de partm nt B xcept f tw pati ts who were admitted t surgi al departments R and D respecti ely Th patient w re selected for the examination on the basis of a clinical susp cion of signifi ant mitral valv dise se A further consideration

[1] In th following krypton" will m an th i otope ^{85}Kr

of formulae for estimating mitral regurgitation as reviewed by Nixon and Snow (1962) The changes described in the time concentration curve can also be produced by increased central blood volume (needle to needle volume) and are found when cardiac output is decreased (Hamilton et al 1931 Korner and Shillingford 1955) Using a dye dilution curve one should accordingly be able to distinguish between slight and severe mitral regurgitation as the latter state would also tend to be accompanied by increased heart size and eventually decreased forward flow However the dye curve would be expected to provide a limited means to distinguish between patients suffering from significant mitral stenosis and significant mitral regurgitation, and this in fact has also been found (Resnekow 1961) Similar difficulties would be expected in evaluation of the degree of mitral regurgitation in patients in severe heart failure Pollssar and Rappaport (1961) concluded a methodological study as follows: As a consequence quantification of atrioventricular valve regurgitation through analysis of a single distal indicator-dilution curve following proximal injection cannot be accomplished"

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estimate at the 95 per cent confidence limit, howeve was still high (24.8 per cent) which was mainly attributed to unrepresentative sampling from the left trium in the pr senc of incomplete mixing of indicator with blood" Another problem using the c ntinuou dye infusion techniqu is whether there is any recirculation from th c ronary artery circulati n (Rahimtola and Swan 1965) and the syst mi circulation through the pulmonary irculation to the left atrium at the tim of equilibrium plateau The difficulty in ttaining a true plateau (as een from fig 2 and 3 in the article of Frank et al 1967) does sugg st this possibility

QUANTITATIVE DETERMINATION BY CONTINUOUS INFUSION OF AN INERT GAS

The advantag of using an inert gas in place of a dye for determination of mitral regurgit tion by means of a c ntinuous infusion techniqu i th t the problem of recirculati n will be diminished, a th indicator will be largely cleared by lungs provided the blood/gas partition coefficient is low The use of a gaseous r dioactiv isotope provid s po sibilitie for easy determination. Lyng... (1965) described the u of th krypton isotope ^{85}Kr) fo this purpose ... minary communic tion; the principl and technique are described be... t al. (1966 1967 and 1972) h e described th u of $^{133}Xenon$ for ... of mitral regurgitati n. The principle in their method w s that ^{133}... line solution w infused into the left ventricl Blood w s simultan... drawn from the l ft trium and a syst m art ry and passed through vett s in close proximity to scintill tion detectors; th output o... w s both printed numeri ally and ecorded on direct writing ... Th recirculation to th pulm nary veins t 60 econds following ... w s stimated to be an ve ag of only 2 3 per cent of the arteria... On arying th position of th tip of th l ft atrial ampling cat... gurgitant fraction w only 2 4 pe cent of th l ft entricular ...

PRESENT INVESTIGATION

MATERIAL

77 p tie t w r selected f examination. They were all ... partment B except f two p tients wh were admitted to ... and D spectively The patient w re selected for the ... of linical suspic of significant mitral val disease ...

*) In th following, krypton will m an the isotope ^{85}Kr

was that they should be able to tolerate the often protracted examination. Thus, patients who were in severe heart failure were not examined Neither were patients examined who had frequent extrasystoles as the presence of a catheter in the left ventricle would increase this tendency and thus cause termination of the examination due to the risk of ventricular fibrillation; furthermore the presence of extrasystoles might c use an "artificial mitral regurgitation.

In 28 cases there were complications which necessitated termination of the examination (the complications will be described in detail later in this chapter) There thus remained 49 patients in whom the examination was carried through.

PRINCIPLE OF DETERMINATION OF MITRAL REGURGITATION

An inert radioactive gas (^{85}krypton) dissolved in saline is infused into the left v ntricle through a catheter which is placed in that cavity by retrograde catheterization. Following a period of 6 8 minutes blood is sampled in sealed syringes through catheters from the left atrium and a systemic artery (the l ft atrial catheter is positioned in the left atrium by an atrial septal puncture technique) The blood is later transferred from the syringes to special cuvettes. The radioactivity of each cuvette is counted by Geiger Müller tubes.

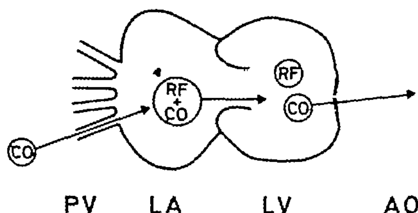


Fig III 1 Diagram showing the flow pattern in mitral regurgitation. Blood enters the left atrium from both the pulmonary veins and the left ventricle and leaves the left atrium for the left ventricle The blood vol me entering the left atrium from the pulmonary veins during one minute s equal to the fo ward cardiac output (CO) During the same period a blood volume eq al to the regurgitant flow (RF) enters the left atrium fr m the left ventricle The blood vol me despatched per minute from the left atrium to the left ventricle is equal to RF + CO

The regurgitant fr ction of the total left ventricular output (RFLVO) can now be calculated from the following equation, assuming that the blood is cleared for krypton through the lung passage

$$RFLVO \quad \frac{CLA}{CSA} \qquad (1)$$

where CLA and CSA are the krypton concentrations in the left atrium and a systemic artery respectively

However, as described later in this chapter, krypton does not escape completely from the blood during the lung passage. Thus the krypton concentration in the left atrium is not only due to mitral regurgitation, but also to recirculation of krypton from the pulmonary artery to the pulmonary veins. Formula (1) accordingly has to be modified as follows:

$$RFLVO = \frac{CLA - CPV}{CSA - CPV} \qquad (2)$$

where CPV is the krypton concentration in the pulmonary veins.

The recirculated krypton (CPV) can be determined by methods described later in this chapter.

DERIVATION OF FORMULA FOR REGURGITANT FRACTION DETERMINATION

In the following, the changes in krypton concentration and flow pattern will be described in a patient suffering from mitral regurgitation. It is assumed that complete mixing takes place in the left atrium as well as in the left ventricle. It is furthermore assumed that no krypton will enter the left atrium except through the pulmonary veins and the mitral ostium and that no krypton will leave the left atrium except through the mitral ostium. It is furthermore assumed that a stable situation has been obtained characterized by a constant krypton concentration in the left atrium. Thus during a minute the same amount of krypton will leave the left atrium as will enter the left atrium (fig. III 1). The following equations can then be established:

$$(CO + RF) \times CLA = RF \times CSA + CO \times CPV \qquad (3)$$

$$LVO \times CLA = RF \times CSA + (LVO - RF) \times CPV \qquad (4)$$

$$LVO\,(CLA - CPV) = RF\,(CSA - CPV) \qquad (5)$$

$$\frac{CLA - CP}{CSA - CP} = \frac{RF}{LVO}\;(= RFLVO) \qquad (6)$$

The equation (6) is identical to equation (2). In the above equations, CO is the forward cardiac output in liters per minute, RF the regurgitant flow in liters per minute and LVO the total output of the left ventricle in liters per minute.

The regurgitant ratio (RFCO), which is defined as the ratio between regurgitant flow and forward cardiac output, can also be calculated:

$$RFCO = \frac{RF}{CO} = \frac{RF}{LVO - RF} = \frac{\frac{RF}{LVO}}{1 - \frac{RF}{LVO}}$$

$$RFCO = \frac{RFLVO}{1 - RFLVO} \qquad (7)$$

The regurgitant ratio can also be calculated directly from the krypton concentration:

$$RRCO = \frac{RFLVO}{1 - RFLVO} = \frac{\frac{CLA - CPV}{CSA - CPV}}{1 - \frac{CLA - CPV}{CSA - CPV}} = \frac{CLA - CPV}{CSA - CPV - (CLA - CPV)}$$

$$RRCO = \frac{CLA - CPV}{CSA - CLA} \qquad (8)$$

The regurgitant fraction can be obtained from the regurgitant ratio as follows:

$$RFLVO = \frac{RF}{LVO} = \frac{RF}{CO + RF} = \frac{\frac{RF}{CO}}{1 + \frac{RF}{CO}}$$

$$RFLVO = \frac{RRCO}{1 + RRCO} \qquad (9)$$

With regard to the above mentioned assumptions, contrast medium is often seen passing from the left ventricle through the left atrium to the pulmonary veins. It is possible that blood with a high concentration of krypton could also pass in some patients from the left atrium to the pulmonary veins. This reflux, however, would not be of any importance if one considered the "left atrium" as that total volume of the left atrium and pulmonary veins able to receive a mitral regurgitant jet; similarly, CPV should be regarded as the concentration in the pulmonary venules. Tattooles et al. (1968) described a case of severe mitral regurgitation with a high left atrial v wave and normal pulmonary resistance, in which the authors felt that blood was passing retrograde through the pulmonary capillaries into the pulmonary artery, since an increasing oxygen concentration was noticed peripherally in the pulmonary artery tree, and since krypton was noticed early in the pulmonary artery following krypton inhalation. A left ventricular cineangiogram, however, did not reveal contrast accumulation in the pulmonary artery. It is accordingly less likely that a krypton "escape" would occur along this route. Another theoretical krypton escape is through the lymphatic drainage of the heart. As the daily lymph production from the heart has been estimated as 1/4 - 1/2 liter (Kluge 1971) the lymphatic drainage is unimportant in this connection. The left atrium receives blood which originates from the coronary artery through the Thebesian veins. Lendrum et al. (1945) determined that the left atrium only received 1.4 per cent of the coronary artery flow. The amount of additional krypton entering the left atrium through the Thebesian veins will thus be small and unimportant in the determination of the regurgitant fraction (RFLVO). The other assumptions described above will be dealt with later in this chapter.

METHOD

The patient was prepared as in the routine for heart catheterization: the patient

was fasting and had been given a sedative (phenobarbiton 200 mg) one hour prior to catheterization. A right heart catheterization was first performed usually through a brachial vein, using a Cournand catheter 7F[1]; during this the presence of intracardiac shunts was excluded by determination of oxygen saturations. Pressures were measured on pull back from the wedge position to the right atrium and cardiac output determined by the direct Fick principle (Fick 1870). A catheter was then introduced into the left atrium by atrial septal puncture using the modification of the technique of Brockenbrough and R[illegible] (1962) described by Lindeneg et al. (1964). In this modification the actual puncture is performed by a thin internal needle[2] as a trial puncture: if left atrial pressure is obtained, the outer blunt needle of usual thickness[2] is also advanced into the left atrium. The left atrial catheter with side holes as well as an end hole at the tip was routinely placed with the tip close to the atrial septum after having described a circular curve inside the left atrium. *The left ventricle was now catheterized retrogradely from the femoral artery* into which the catheter had been introduced by the technique of Selding[illegible] (1953) using a Lehman catheter 7F or 8F[1]. A Lehman catheter 4F[1] had often to be introduced through the Lehman catheter 7F in order to pass the aortic valve or to avoid premature beats. A small polyethylene catheter (Polystan 52 A)[3] was finally inserted into a systemic artery also by the technique of Seldinger (1953). The pressure in the left atrium and the left ventricle was measured routine simultaneously except for a few cases where pullback curves were used. For connection between sampling catheter and sampling apparatus polyethylene catheters (Polystan 53 A)[3] were used.

Infusion of a krypton solution prepared prior to the examination was then started. Blood samples of approximately 5 ml were now taken into tightly fitting syringes through the use of a specially designed apparatus for simultaneous sampling[2]. Samples obtained simultaneously from a systemic artery and the left atrium (and the pulmonary artery) were thus available. Prior to the sampling approximately 10 ml of blood had been withdrawn by another syringe which was connected to the sampling syringe by a 3 way valve. During the infusion the left atrial catheter or the infusion catheter was gradually pulled back in order to obtain different positions for the tip of these catheters. At the end of the examination the infusion catheter was pulled back to the aortic root. Following a period of approximately 6 minutes samples were again taken. Finally the infusion was stopped. Samples were now again obtained following a period of approximately 5 minutes.

A small volume of gaseous krypton[4] containing 30 mC was equilibrated with 0.9 per cent saline in a 100 ml oiled glass syringe. Saline from this solution con

1) United States Catheter and Instrument Corporation, Glenn Falls, N.Y. 12801 U.S.A.
2) O Dick, Avedør holmen 18 2650 Hvidovre Denmark.
3) Polystan, Gene[illegible]vej 41 2750 [illegible] Denmark.
4) obtained from The Radiochemical Centre Amersham Buckinghamshire England

taining approximately 1 mC was transferred to 0 9 per cent saline which was kept in two different 100 ml oiled glass syringes The contents were mixed by a mag netic stirring rod The syringes were used for simultaneous infusion, the infusion rate being 7 ml/minute

Prior to the examination the syringes for sampling were wetted inside with heparin saline (1000 units per ml) leaving no air in the syringes After the blood samples had been obtained the syringes were rotated mechanically Shortly fol lowing this the sample was transferred from the syringe to a specially designed cuvette without access to air These cuvettes were designed and described by Lassen and Munck (1955) They are disc like with a steel ring and thin walled sides of plastic and contain 2 5 ml blood each. Each cuvette has two studs for transfer of blood Each stud is fitted successively with a 1 cm rubber tubing a 1 cm lead tubing and a 1 cm rubber tubing The cuvettes are sealed by clamping the two lead tubings When filled the cuvettes were placed horizontally and the blood allowed to sedimentate for at least one hour The radioactivity in each cuvette was counted as de cribed by Lassen and Munck (1955) The cuvettes were placed horizontally on a rotating disc[2] which was able to hold 18 cuvettes *Using the rotating disc first des gned each sample was counted for a predetermin ed time* In the later design each sample was counted until a predetermined num *ber of counts had been r ached*

The samples in each cuvette were counted from each face of the cuvette with *two Geiger Müller tube* which were placed verticall) above *and below* the sample Each Geiger Müller tube was powered by the same voltage and the impulses were *fed into the same scaler* The rotating disc hanged automatically *from one* speci men to anoth r Each uvette wa ounted for a sufficiently long period to make the *statistical error l than 5 per cent Each sampl wa corrected* for back ground activity and dead tin e error The ba kground activity was an aver ge of 35 CPM *All me surement f background activit except f r tw were below* 50 CPM the two highest value we e 74 and 87 and obtained on success ve exam inations *The average arterial concentration wa 8 7 CPM varying betw en* 61 and 5576 CPM ^{85}Kr w s selected f r use in this stud as krypton has a low blood/gas *partition coeff ient* (0 08 Mell *rngaard et al (1961)*) and as krypton was used for other purpo es n our labor tory (determinat n of myocard al per fusion) ^{85}Kr is w k bet *emitt r whi h al he gan ma radioact v ty* Th latter is only 0 5 per nt f the beta acti it The uvettes re pec ally de signed to allow p ssage of bet *ad t on. Th sol b l t f krypt n is higher* n erythrocytes than in pla ma (an Slyk et al 1934) the amples are theref r counted both from abov and b l w

The rad ati n dos to the patient du ng the xam nat on small bec use of the short bi l gi al half l fe f ^{85}Kr (Las n and Munck 1955) The maximal radiation d se from intra enou njection of 1 mC ^{85}K can be calculated from

---

2) O Dick A ed reholmen 18 2650 Hvid vr D nm rk

table 4 of Lassen (1965): tracheal mucosa 14 5 mrad, lung 5 5 mrad adipose tissue 0 8 mr d, gonads 0 1 mrad oth tissue 0 1 mrad (this is an estimate of the maximal dose as an amount l than the t tal of th krypton-c ntaining infu si n solution was used in m st of the examinations) The p tient will thus receive smaller radiation dose from th ^{85}Kr u ed in this examination than if h had an ordinary ch st roentgenogram taken. Th dose to the gonads i smalle than the natural background radiation received in one day

EVALUATION OF RECIRCULATION OF KRYPTON FROM THE PULMONARY ARTERY TO THE PULMONARY VEINS

In the above mentioned equati n (2) an important factor is the krypton concen tration in the pulmonary v ins during krypton infusi n int the left v ntriol In this study the recirculation ha been examined by tw methods: In ituation K" krypt n w s not inf sed into the left ventricl but into th ortic root. Provided that no orti im mpet nce was present (th p ti nts did not hav any murmur suggesting thi disease) the krypton c ncentration in th left trium would thu be identi al with that in the pulmonary veins; th ecirculation of krypton ould now be det rmined from the krypton conc ntr tion in the pulmonary art ry and the left trium, respectively In situ ti n L th concentration f krypton in the pulmonary art ry and the l ft atrium w s followed f 6 8 minute afte the krypt n infusi n had been stopped. F llowing an initial wash-out period, th krypt n c ncentration in the left trium would be identi al with that in the pulm nary veins; th ecirculation could acc rdingly now gain be determined from th krypt n conc ntrati n in th pulmonary art ry and th left trium

Th se e aminations w re carried out d scribed in Method" Thu the ample f situ tion K w taken afte withdr wal of th infusion c theter to the sc nding aorta. I situ tion L the sampl were tak aft discontinuati of the inf si n. In the latt tu tion the krypton concentr tion will be high r in th pulmonary rtery than in the pulmonary veins du t the slow wash out of kryp ton from th ti sues of th body well as to th sc pe of krypton through the lungs.

RESULTS AND COMMENTS REGARDING KRYPTON RECIRCULATION

Fo ch sampling per od (one minute) ati an be calculated betwe n the krypt n concentr tion in th l ft trium and that in the pulmonary artery

In table III 1 thi ecirculati n rati (REC) is listed for ach patient in situa ti n K and L

If th average is calculated only for th se pati nt in whom examinations were carried out both in situ tion K and i situ tion L th averages are 0 116 (SD

Table III 1 Recirculation ratio in individual cases

C s N	itu ti n K	itu ti n L
5061	0 128	0 235
5577	0 118	0 158
7840	0 124	0 133
7758	0 115	-
6757	-	0 321
3645	0 105	0 140
5492	0 072	0 107
7543	-	0 181
5295	0 074	-
5837	0 097	0 189
8314	0 077	0 112
8050	0 143	0 170
8042	0 210	
5078	-	0 277
6688		0 262
3746	0 181	0 179
4965	-	0 389
7009		0 082
5226	0 092	0 122
7664	0 095	0 099
6322	0 133	
8093	0 200	0 270
6010	0 072	0 083
3756	0 108	0 216
8013	0 036	0 002
6660	0 067	0 115
7815	0 150	0 201
5068	0 108	0 116
914		0 286
A g	0 115	0 178
7347	0 137	

0 041) and 0 154 respectively (SD 0 060) thi difference in averages i signi ficant (p < 0 01) The re son for thi difference that sit atio K and L repre sent different condition n the pulmonary c pillary alveolar g s e hange In situation K the conditions are rather stable Only a slight decrease occurs in the

left atrial concentration, and a similar slight increase occurs in pulmonary art ry concentration; th differenc between capillary conc ntr tion and room concentra tion is large and fairly stable In situati n L the condition is not stable th pul monary art ry c ncentration and left atrial concentrati n are dec sing apidly the difference between pulmonary pillary concentration and room concentrati n being al tively smaller and decreasing It should furthermore b noted that situ tion K is similar to the condition during regurgitant flow det rmination (the condi tion being rather stable in both circumstances and the pulm nary artery onc n trati n slightly increasing) however th left trial oncentration will be slightly decreasing in situation K wh re it will be slightly increasi g during regurgitant flow det rmination. Finally it should be mentioned that as th l ft atrial onc tration and particularly th pulm nary art ry conc ntr tion will be c nsid rably higher in situation K than in situation L the ccuracy of the recircul tion deter mination in situation K will be considerably greater than in situ tion L

Table III 2 Ratio between REC at indi ted tim int rval and REC at 8 minut s tim interval

	REC ti							
T me i t rv l (mi t) →	4	5	6	7	8	9	10	11
Si ti K	1 54 (2)	1 33 (2)	1 15 (9)	0 99 (13)	1 00 (18)	0 84 (14)	0 81 (9)	0 74 (5)
S t ti L			1 14 (11)	1 10 (17)	1 00 (21)	1 02 (16)	1 04 (8)	0 98 (2)
C 7347		1 12	1 05	1 09	1 00	1 00	0 98	-

Th tim interval alculated from start f rtic inf sion or from stop f inf ion, respecti ely
Th number in parenth si indic te the number of patient
REC (ecircul tio rati) the rati between l ft trial concentration (CLA) and pulmonary rtery concentrati (CPA)

Tabl III 2 show f r s tu tions K and L th atio between REC val es at diff ent indicated time int rval rel ti e t th REC valu t 8 minut after the start of aorti inf sion aft the stop of infusion, r specti ely As seen from the numbers definit dec e s in REC w th tim wa present in situ t on K, in situation L dec e REC could not be proven. Case 7347 i a niqu o se s there w no krypton inf sion into th l ft ventricl pri t th ortic infusion.

Th xpl nation f thi trend is seen from tabl III 3 which shows the trial

and pulmonary artery concentration at different indicated time intervals relative to the concentration 8 minutes after the start of aortic infusion or after the stop of infusion, respectively In situation K there is an increase in pulmonary artery concentration as well as a decrease in left atrial concentration. The cause of the increase in pulmonary artery concentration (CPA) in situation K is most likely the interruption of infusion during pull back of the infusion catheter from the left ventricle to the aorta, during this period CPA is decreasing later an increase in CPA would be expected when the infusion was continued The duration of this interruption was not measured but probably lasted an average of 2 minutes.

Table III 3 Ratio between krypton concentrations at indicated time intervals to concentrations at 8 minutes time interval

		[illegible]						
	time interval (minutes) →	5	6	7	8	9	10	11
Situation K	pulmonary artery	0 78 (2)	0 93 (9)	0 98 (13)	1 00 (17)	1 09 (14)	1 07 (8)	1 12 (4)
	left atrium	1 00 (2)	1 07 (9)	1 01 (13)	1 00 (17)	0 93 (14)	0 88 (9)	0 90 (4)
Situation L	pulmonary artery	1 45 (2)	1 31 (12)	1 17 (20)	1 00 (23)	0 90 (18)	0 79 (11)	0 75 (5)
	left atrium	1 95 (2)	1 93 (12)	1 48 (20)	1 00 (23)	1 05 (18)	0 89 (10)	0 73 (3)
Case 7347	pulmonary artery	0 57	0 81	0 91	1 00	1 11	1 17	
	left atrium	0 63	0 85	0 98	1 00	1 11	1 15	

The time interval is calculated from start of aortic infusion or from stop of infusion, respectively
The numbers in parenthesis indicate number of patients examined

In situation L a similar decrease in krypton concentr tion was seen in both the l ft atrium and the pulmonary artery thus explaining the l s pronounced and questionabl decreas in REC in thi situation (table III 2) In e 7347 the in crease in l ft trial concentr tion wa very similar to that in the pulm nary artery

Tabl III 4 C mparison between REC rati t indicated time int rvals in patients with a larg and with a small regurgitant fraction. (S tu tion K)

	REC ti					
Time int l (min t) →	5	6	7	8	9	10
RFLVO > 0 40	1 10 (1)	1 23 (2)	1 14 (3)	1 00 (6)	0 79 (5)	0 73 (4)
RFLVO < 0 10	1 12 (1)	0 91 (3)	0 92 (6)	1 00 (6)	0 88 (6)	0 90 (4)

This table is similar to tabl III 2 Thu the number in parenthes indicat the numbe of p tients.
REC (ecirculation) th r tio between l ft atrial concentration (CLA) and pul monary art ry c nc ntrati (CPA)

Table III-4 d scribe th recirculati n tio (REC) in tu tio K f llowing pull back f th infusi n thet t th aorta in p ti nt with a large and with a small egurgitati n. It n f om thi tabl that th recirculation i apparently st bl 6 minutes after th withdr w f th thet r to th aorta if th regurgita tio small but decr with tim if the regu gitation is large

T bl III 5 confirms th correlation betw en regurgitant fraction (RFLVO) and rec rculati n (REC) It ee from tabl III 5 that no rel tion ould b d monstrated betw en ec rculation r tio (REC) and a numbe of variable notably ardi c olum ind (CVI) ardia nd (CI) and l ft atrial mean p essur (LAMP)

Th recircul ti n r ti (REC) w s found to be an average of 0 092 for pati nts h ving a mall regu git ti n and 0 136 f r p tients having large regurgitation. Ac rding t th above d scribed corr lation betwe REC and regurgitant f ac ti (RFLVO) th l tt val e f 0 136 m st be regarded s e oneously high th rro be ng du t the slow w sh out of th left atrium ec ndary t the larg p ndulum vol me The f rm REC val of 0 092 i similar to that found by C hid y et al (1959)

T bl III 6 repre nt the sult f an evalu tio f th effect of different

values of recirculation ratio (REC) on the accuracy of the regurgitant fraction (RFLVO) determination. The latter is calculated from the formula

$$RFLVO \quad \frac{CLA \quad CPV}{CSA \quad CPV}$$ (equation (2) of page 43)

Table III 5 Examination for correlation between REC and indicated variables.

V ri ble	n	R	p
R g git nt f cti n (RFLVO)	24	0 58	0 003
Left t i l width (LAW)	15	0 42	0 12
Art i l ca bon di ide t nsio (PCO_2)	10	0 37	0 30
Left atri l me n pre s (LAMP)	24	0 20	0 35
Ca di c ind (CI)	21	0 18	0 42
Cardi v l me i d x (CVI)	23	0 12	0 60
Pulmo ry v c la r i t n (PVR)	21	0 11	0 62
Art ri l xyg t ti	24	0 10	0 66

R th c r l tio ffi i t f Sp m

For each simultaneously obtained CLA CSA and CPA value RFLVO is calculated using two different methods for determination of recirculation, listed as recircul tion determination method x and y (these methods are described below) The u e of two methods for determination of recirculation will thus give two RFLVO values for each set of simultaneously obtained CLA CSA and CPA values The sum of the two valu s is listed to the left in table III 6 the difference between the *two RFLVO values is listed* according to the two methods used *for determination.*

In the calculations marked REC K for each sampling period of 1 minute s *duration, the regurgitant fraction (RFLVO) for that period is calculated using* the CLA and CSA value of the period, CPV is taken as the product of CPA for that period and the ecirculation ratio (REC) for the individual patient obtained in situ tion K

Calculati n of the regurgitant fraction (RFLVO) in the calculations marked REC L was performed as in those marked REC K' except for CPV being calculated a the product of CPA and the rec rcul tion ratio (REC) obtained in situation L

In the calculations of the regurgitant fraction (RFLVO) marked 0 00' 0 05 0 1 0 2 and 0 3' respectively RFLVO w s calculated as for REC K except that CPV was calculated th p oduct of CPA and 0 00 0 05 0 1 0 2 and 0 3 respectively

Table III 6 C mpar ti xamination of the ffect of sing different recircul tion tion (REC) i alcul t ng gurgitant fraction in the sam p tient

Limit f um f gurgitant fractions l l tion usi g y method f ecirc det	Reci det rm. method	Diff r b tw al l t d RFLVO v l (bt i d by r cir l tio th d d y p ti ly) A SD d n mb f RFLVO lc lt ti n								
	→	REC K	REC K	REC K	REC L	REC L	0	0 05	0 2	0 3
	y →	0 1	P-V	REC L	0 1	P-V	0 1	0 1	0 1	0 1
		0 010	0 021	0 023	-0 018	-0 109	0 066	0 034	-0 082	-0 178
<0 05		0 016	0 026	0 031	0 044	0 038	0 018	0 009	0 023	0 052
		(49)	(52)	(51)	(72)	(56)	(39)	(53)	(125)	(149)
		0 008	0 013	0 012	-0 009	-0 006	0 060	0 035	-0 067	-0 131
≥0 05 <0 10		0 021	0 022	0 017	0 032	0 025	0 021	0 012	0 025	0 057
		(33)	(32)	(30)	(43)	(35)	(23)	(30)	(17)	(14)
		0 005	0 003	0 026	-0 026	-0 020	0 070	0 035	-0 066	-0 129
≥0 10 <0 25		0 022	0 013	0 031	0 040	0 043	0 017	0 009	0 021	0 036
		(42)	(45)	(55)	(63)	(45)	(85)	(70)	(39)	(37)
		-0 013	-0 002	0 078	-0 078	-0 061	0 053	0 027	-0 056	-0 119
≥0 25 <0 50		0 022	0 011	0 063	0 085	0 076	0 015	0 008	0 016	0 038
		(36)	(33)	(30)	(38)	(32)	(69)	(65)	(51)	(36)
		-0 008	0 005	0 044	-0 043	-0 027	0 042	0 021	-0 044	-0 091
≥0 50 <1 00		0 026	0 019	0 029	0 041	0 038	0 013	0 007	0 015	0 033
		(59)	(61)	(48)	(66)	(46)	(78)	(80)	(73)	(76)
		-0 013	0 003	0 034	-0 033	-0 009	0 018	0 009	-0 020	-0 041
≥1 00 <2 00		0 011	0 011	0 010	0 030	0 018	0 011	0 005	0 012	0 025
		(68)	(64)	(55)	(103)	(55)	(129)	(125)	(118)	(111)

When the regurgitant fraction (RFLVO) was calculated for the samples marked PV' RFLVO was calculated as for REC K' except that the average CLA value obtained during aortic root infusion for each patient was used as the CPV value.

When comparison of two methods of recirculation ratio (REC) calculation was made (and these two methods were thus used for determination of the regurgitant fraction (RFLVO)) this demanded that CLA and CSA values were available for that sampling period (and if necessary also a CPA value) a well as REC values obtained in situation K, L or PV' respectively for that particular patient

From table III 6 it is apparent that it is of little importance in the determination of the regurgitant fraction (RFLVO) whether the recirculation ratio (REC) is calculat d by the use of any one of the following factors "0 0' "0 05 0 1 "0 2' or REC K" except for small regurgitant rates (X + Y < 0 10) Only if the recirculation ratio was as high as 0 3" or factor REC L was used, was the accuracy of the regurgitant fraction (RFLVO) determination significantly affected. Regarding the calculation of small regurgitant fractions (RFLVO) the inaccuracy of the regurgitant ratio (REC) determination l ads to incertitude as to which number for the regurgitant fraction is the correct one For practical purposes however it is r rely important whether a minimal regurgitation is pre ent or not, neither is the exact determination of a minimal regurgitation usually of practical importanc

In this study the regurgitant fraction will be calculated using as CPV the product of 0 1 and CPA. If the l tter has not been obtained then the average of the left atrial concentration d ring aortic root infusion will be used as the CPV

CONCENTRATION CHANGES DURING INFUSION

T ble III 7 shows the changes in krypton concentration in a systemic artery the l ft atrium nd the pulmonary artery following start of infusi n (see also fig III 2) For each minut the concentration is calculated relative to the oncentration 6 minute following start of infusion, the average being given for the number of patients ind ated together with the standard deviation (SD) F r the systemic artery and l ft atrial concentr tion a level is reached within 6 8 minutes; in 4 minutes the concentration is 80 90 per c nt of the concentration at the horizontal portion of th curve From th amples examined no proof can be demonstrated of any further ncre a n concentration later than 6 8 minute from the start of infus on. In the pulmonary art ry th horizontal oncentrati n level is reached later than n the sy temic artery or in the left atrium the examination sugg st but does not p ove that plate u h e been re ched after 11 12 minutes The concentrations in the pulmonary artery at 4 6 and 9 minutes are 46 69 and 91 per cent respectiv l of the pulmonary rtery concentr tion 12 minutes after start of infusion.

For det rmination of the regurgitant fraction, ampling earlier than 4 minutes

Table III 7 Relative krypton concentration changes during inf si n,

Int rv l ft t t f i f i (mi t)	Sy t mi t ry	L ft t i m	P lmo ry rt ry
1	0 04 (0 041 - 4)	0 05 (0 048 3)	0 06 (0 017 - 2)
2	0 57 (0 162 4)	0 36 (0 151 4)	0 20 (0 168 - 3)
3	0 82 (0 043 4)	0 69 (0 234 4)	0 37 (0 108 3)
4	0 82 (0 189 9)	0 89 (0 129 9)	0 66 (0 235 - 9)
5	0 86 (0 179 10)	0 96 (0 074 - 10)	0 86 (0 087 9)
6	1 00 (11)	1 00 (- 11)	1 00 (- 10)
7	0 98 (0 083 10)	1 06 (0 101 10)	1 13 (0 133 9)
8	1 04 (0 067 9)	1 11 (0 143 9)	1 26 (0 132 - 7)
9	1 02 (0 048 8)	1 13 (0 146 - 8)	1 32 (0 127 5)
10	1 02 (0 060 3)	1 02 (0 089 - 3)	1 26 (0 066 3)
11	1 02 (0 032 3)	1 11 (0 103 3)	1 51 (0 333 3)
12	1 02 (0 066 3)	1 12 (0 148 3)	1 45 (0 137 - 3)
13	1 05 (1)	1 04 (1)	1 87 (1)

Th main number indicat the rati between the noentr tion at the indi ated tim and the concentration 6 minut following start of infusion. The first num ber in the parenthesis i SD the other i th number of patient used in th cal culati n.

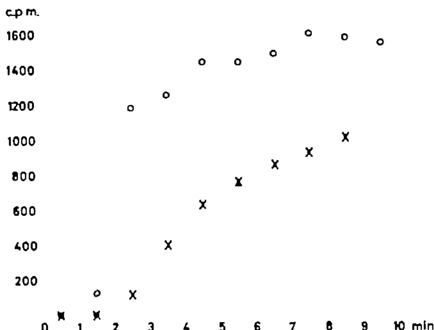


Fig III 2 Di gram sh wing the krypton concentration in a systemic artery (o) the left atrium (•) and the pulmonary artery (x) following start of infusion (0 mi nutes) in a patient with significant mitral regurgitati n.

will decre se the a curacy of the determination, as the oncentrations at all 3 sampling sites will lie on the rapidly ascending c rves Determination of the regurgitant rate 4 8 minutes following start of infusion will introduce an error of importance only in the determinat on of mall regurgitant fractions (RFLVO) via the indirect effect of rising pulmonary artery concentration. Following 8 minutes infusion, no signif cant errors will be introduced in the regurgitant fraction de termination as result of time dependent concentr tion changes

It should however be noticed that the evaluation of concentration changes with tim in thi study is based on a limited number of patients This is parti cularly the garding the early and the late changes where only 3 patients have been examined The difference betwe the increase in concentration in the l ft atri m and the syst m rtery is probably not significant th absolute concentration i f r low in the atrium than in the ystemic artery

Similar results regarding con entration change in the pulmonary artery have been found by Lindeneg (1973) who used nhaled krypton fo d termination of coronary blood fl w A pl t in the pulm nary artery c ncentrati n was sually reached 15 minut after st rt of inhalation.

EVALUATION OF ERROR IN A SINGLE DETERMINATION OF REGURGITANT FLOW

Table III 8 show the chang s in conc ntration within a situation (a situation is de

fined as a sampling period during which the catheters were located at th ame sit and th infusion rate wa constant) Within each situati n, sampling was thu continuou and consisted of several ampling period each lasting one minute Between two situations however the sampling was interrupted and thu discon tinuous. In the table the concentration in samples taken 1 minute foll wing start of ampling i mpared to the concentration in sample taken 2 minute following start of sampling, sample taken 2 minute afte start ar ompared to samples taken 3 minutes after start, et It will be een th t for th systemi art ry and left atrial sampl an average increase of 4 per ent p r minute was found during th first 3 minutes. In th pulm nary artery the average increase for the first 3 minute i similar to that in the left atrium and syst mi art ry Th inc ease from the 4th t the 5th minute is howeve larg (22 pe ent) possibly repre enting sampling in a selected group of patients

As se n in table III 8 the ncrease in krypton concentration during ampling from the systemi art ry i gre ter than expected from the almost onstant systemic artery concentrati ns see through th time interval 6 t 12 of table III 7 (during the examinati ns f table III 7 sampling was ntinuous) A possibl use of th in rease seen in table III 8 is th diluti n ffect of saline present in the sampling thetors and th plastic tube connecting th th ter to th sampl ing apparatus, despite th fa t that 5 10 milliliter of blood w tak from th theters befo e sampling Lindeneg (1973) h exami ed th inc se in krypt oncentration during ampling from taine filled with blood ha ing a unif rm krypton conc ntrati n, Using th am sampling method as in thi study h found that the sampl tak n 1 2 and 3 minute aft sampling started o tained on the av rag 8 6 and 1 per ce t, respectively l krypton than that of the container He acc rdingly ecommended th t 10 millilit f blood should be withdrawn and not used as ampl R garding the sampl s from the l ft trium and th pulmonary art ri t is mo difficult to ompar table III 7 and III 8 as th real pulmonary art ry conc tr tion ignifi antly incre sing in the former table but probably ot t the tim f the latte s ampling then occurred mainly t the h rizontal part of the nc ntration curv

As a on eq nc f the hang in krypt n conc ntrati n d scribed above th effect of th se chang n th egurgitant fr cti n (RFLVO) determination wa e amined. Tabl III 9 show th ave age diffe ence b tween th calcul ted RFLVO valu f two con ec tiv ampling period

As seen from th tabl th av ag val show only small change with tim Thi i du t the similar ty of the chang in the ncentr tions with time in the syst mic artery l ft tri m and pulm nary artery (t bl III 8)

T bl III 9 however also show that th standard deviations of th calculated RFLVO diff renc ar relatively high

I tabl III 10 the diff renc is calculated betw en th first minute RFLVO val in e ch situation and th l ter val in the same situation. Th finding listed according to the siz of RFLVO as det rmined by the first minute

Table III 8   Relative change in concentration during continuous sampling

Sampling period sampled		Sampling sites	Relative change in concentration within a situation		
A	B	→	Left atrium	Systemic artery	Pulmonary artery
2	1		0 07 (0 017 115)	0 04 (0 014 131)	0 06 (0 017 - 91)
3	2		0 04 (0 017 119)	0 04 (0 003 126)	0 06 (0 003 - 91)
4	3		0 01 (0 003 55)	0 05 (0 003 - 58)	0 001 (0 014 - 40)
5	4		0 03 (0 014 12)	0 03 (0 014 - 13)	0 22 (0 022 - 9)

The main number is calculated as the average of $\frac{\text{concentration A} \quad \text{contentration B}}{\text{concentration B}}$

The first number in the parenthesis is the standard deviation, the last number the number of situations examined   For further explanation see text.

Table III 9 Changes in gurgitant fraction (RFLVO) during contimou ampling within one situation,

S mpli g p i d A	mp d B	Ch g in RFLVO	SD	n
2	1	0 01	0 089	112
3	2	0 01	0 088	110
4	3	0 01	0 042	49
5	4	0 01	0 019	11

Th elative chang in RFLVO i alculated as $RFLVO^{A}$ $RFLVO^{B}$ wh r th lett A o B indicat th sampling period used

Tabl III 10 Comparison betw en RFLVO valu within each situation ac rding t siz of RFLVO

Si f RFLVO[1] X	RFLVO diff v g	SD	n
X < 0 05	0 01	0 016	84
0 05 < X < 0 25	0 01	0 064	86
0 25 X 0 50	0 06	0 146	47
0 50 ≤ X < 0 75	0 01	0 100	35
0 75 X < 1	0 02	0 061	17

RFLVO[1] th RFLVO of th first sampling period within ach situ ti n. The v ag RFLVO diff renc cal ul ted as th diff renc between the RFLVO[1] and RFLVO f any oth sampling p riod within the am situati n.

val in ch situ ti n. Th verag diff nc seen to be quit small the nly xcepti n being th group h ving an RFLVO val b twe n 0 25 and 0 50- this group al o h the highest SD It s again noticed that the standard deviations listed are high ex ept f small regurgitant fractions (RFLVO ≤ 0 05)

Tabl III 11 Deviation fr m mean RFI VO within each situation Distribution according to size of deviation for v riou l v ls f m an RFI VO

Me RFLVO x	D i ti n from m of ituati n								Total	
	0 30	0 10	0 05	0	0 05	0 10	0 30			
				n	n	n	m	m	n	SD
x < 0 05	0	0	0	60	67	0	0	0	127	0 010
0 05 < x 0 25	0	0	3	70	67	0	1	0	141	0 027
0 25 x < 0 50	0	1	4	21	24	4	2	0	56	0 055
0 50 < x < 0 75	1	6	11	15	13	9	9	1	65	0 131
0 75 < x	0	1	4	12	15	2	1	0	35	0 061
	1	8	22	178	186	15	13	1	424	0 049

Table III 12,

Table III 12 Number f sampl e d vi ting from median val e within one situation, Distribution according to it f mpli g and i e f d vi ti n,

D i ti f m medi 1

0 30 0 10 0 05 0 0 05 0 10 0 30

									Tt l n	SD
L ft t i m	8	22	27	62	111	29	27	4	290	0 145
Sy t i t y	2	38	53	107	212	48	28	4	492	0 130
P lmo y t ry	10	28	26	70	131	35	31	2	333	0 118

The groups are arranged ccording t the devi ti n from th median valu as expressed rel tive to the si e of the median value

In table III 11 this is examined further In this table the reference is the mean RFLVO value within each situation. Each RFLVO determination is listed according to its deviation from the mean and according to the size of the mean RFLVO- the standard deviation for each group of the mean RFLVO is also described It is seen that the distribution ppears to be rather similar to a normal distribution curve and that the high standard deviations are not merely due to single RFLVO determinations deviating extremely from the mean value

Table III 12 was constructed to examine whether this high standard deviation of the RFLVO values within a situation was due to the concentrations varying particularly much at certain ampling sites Here the reference value is the median value at each sampling sit and in each situation. The deviation from the median val e of other samples in the same situation was expre sed relative to the size of th median value Again a high SD was found which was not due to the extreme deviation of single samples It is also seen that the SD is very similar at each sampling site The cause of the high standard deviations is not obvious Contamination" with air is possibly a contributing factor

In concl si n. The standard deviation of single RFLVO determinations was found to be high although the significance of this finding is decrea ed by the fact that the higher SD occurred only for higher RFLVO values (RFLVO > 0 25) Accordingly it i advisable t t ke 3 samples from each sampling site in each situation and use their average for RFLVO determination. As seen from the average values of table III 10 the error in RFLVO determination will then be cceptable Sampli g should not begin earlier than 6 minute after start of infusion. Similarly sampling for estimation of recircul tion should first take place 6 mi utes after start of aortic infusion.

EVALUATION OF THE ERROR DUE TO THE SITE OF LEFT ATRIAL SAMPLING

In order to evaluate thi the tip of the left atrial catheter was placed successively in four diff rent po tions in the left atrium (fig III 3):

A clo e to the nteratrial septum as cephalad a possible
B clo e to the interatrial eptum a caudad p sible
C as close s po ible t the mitral ostium
D: midway betw e positi n A and th l ft wall of the left atrium

Usually thes position w re obtained by the c theter first being pl ced in position A. The cathet r nd tip were then pulled back stepwise from po ition A → B → C → D Th po iti of the c thet r tip w checked by flu roscopy and described in the ch rt. I most s (27) a cinefilm (without contrast injection) w s taken of the diff nt th t t p po iti n The film w re tudied and used for classific ti n. I o t \ d B w re us ally e sil identified P i

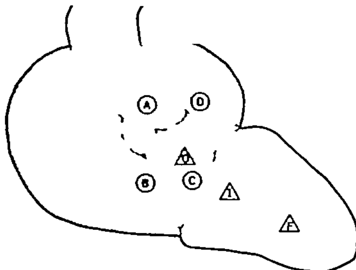


Fig III 3 Diagram showing the sites of sampling in th left atrium (Ⓐ Ⓑ Ⓒ Ⓓ) and the sites of infusion into the left ventricle (△.△ △)

tions C or D were mor diff cult to distinguish. Occasionally the c theter tip was seen travelling spontaneously from po tion D to C during an examination. If the cath ter tip position wa not rec rded r no film was available th position was registered E

Table III 13 ecord th r sults of thi examination. Th calculated av age regurgitant fra ti n val (RFLVO) is listed in ach position for each patient. For each patient th m an RFLVO of all left trial positi ns i also listed with the standard deviati n (patients have only been listed if at least 2 left atrial positions h ve b en obtained and if within e h position (situ ti n) at least 2 RFLVO values have been obtained) If th l ft atrial positions are compared two and two regarding RFLVO n statisti ally signif cant differenc is found (table III 14) using ank sum t st ($p > 0\ 05$ for all situations except between situation C and E where $p < 0\ 02$)



Fig III-4 Diagram showing the numb r (n) of patients with the sam standard de diation (SD) f regurgitant fracti n (RFLVO) determinati n.

Table III 13 Regurgitant fraction at different catheter tip positions in the left atrium

Case No	Catheter tip position → A	B	C	D	E	Mean RFLVO	SD
	Regurgitant fraction (RFLVO)						
7801	0.40	0.40	-	0.37	-	0.387	0.02
7840	0.07	0.06	0.07	0.06	-	0.061	0.01
7758	-	0.23		0.27	0.29	0.263	0.03
3645	0.33	0.37	0.28	0.26	-	0.317	0.07
5492	0.04	0.04	0.10	0.05	-	0.059	0.03
8314	0.03	-0.02	0.02	0.01	-	0.021	0.01
5226	0.06	0.04	0.06	0.06	-	0.052	0.01
6322		0.52	-	-	0.60	0.586	0.02
6010	0.03	0.02	0.05	0.02	-	0.027	0.01
3756	-0.02	0.01	0.02	0.00	-	0.012	0.08
6660	0.22		0.31	0.20	-	0.246	0.06
7815	0.16	0.18	0.22	0.14	-	0.173	0.03
5068		-	-	0.02	0.10	0.062	0.05
5837	0.33	0.23	0.22	0.48	-	0.315	0.12
8560	0.14	0.21	-	0.17	-	0.174	0.03
6595	0.53	0.58	0.52		-	0.541	0.03
5061	-		0.78	0.73		0.734	0.03
5977	0.68	0.82	0.87	0.96		0.835	0.12
4054	0.76	0.58	-	0.60	0.63	0.604	0.03
6757	0.84	0.86	-	0.74	0.93	0.835	0.10
6191			1.41	0.90	0.74	1.019	0.38
7543	0.05	0.07	0.70		0.10	0.271	0.37
3855	0.00	0.00	0.00	0.02	-	0.006	0.00
8050	0.60	0.69		0.69		0.660	0.05
8042		0.43		0.38	0.33	0.376	0.05
3422		0.06	0.19	0.20		0.149	0.08
3746	0.67	0.62	0.62	0.62		0.633	0.02
7009	0.03	0.03	0.03	0.03	0.02	0.028	0.00
0666			0.03		0.02	0.022	0.00
8591		0.03		0.45	0.24	0.242	0.21
7664	0.02		0.15	0.03	0.01	0.053	0.02
4465				0.18	0.14	0.157	0.03
4253		0.02	0.00	0.03		0.001	0.01
8093	0.68	0.74	0.97	0.64		0.760	0.15
1682		0.10		0.14		0.121	0.03
914	1.00	0.89	0.75	0.90	0.71	0.849	0.12

For explanation see text.

A further analysis of the standard deviation is shown in fig III-4 which is a sc tter plot of number of patients ve su SD of RFLVO determinati n. The scatter plot shows that the number of patient decreases with incr asing SD. it is noti ed that two patients have high SD of more than 0 30- CL 6191 and CL 7543 Figure III 5 1 a scatter plot having the mean RFLVO as absci sa and SD ordinate It is is seen that two patient have a signif cantly high SD again as CL 6191 and CL 7543

T bl III 14 Comp rison between RFLVO for diff nt left trial positions

P iti	mp d	R nk m	P
A ⟷ B	22	154 099	> 0 05
A ⟷ C	19	130—060	> 0 05
A ⟷ D	22	145 108	> 0 05
A ⟷ E	07	019 009	> 0 05
B ⟷ C	20	147 063	> 0 05
B ⟷ D	25	198 127	> 0 05
B ⟷ E	11	034 032	> 0 05
C ⟷ D	21	142 099	> 0 05
D ⟷ E	11	041 025	> 0 05
C ⟷ E	8	035 001	< 0 02

SD

0 50

0 40

0 30

0.20-

0 10

0 10 0 0 10 0.20 0 30 0 40 0 50 0 60 0 70 0 80 0.90 1 0

RFLVO

F g III 5 Relationship between st ndard deviation (SD) of regurgitant fraction det rmination and egu gitant fraction (RFLVO)

In case 6191 the large SD is mainly due to an RFLVO value of 1 4 If this value was correct flow from the left ventricle to the left atrium would be 40 per cent higher than the total left ventricle output and this is impossible An alternative explanation would be that the infusion catheter had been placed in the vicinity of the mitral ostium and th t the krypton w s infused almost directly into the left atrium Another explanation is that the left atrial catheter had fallen into the left ventricle the sampling being performed close to the tip of the infusion catheter In case CL 7543 the concentration at the catheter tip position close to the mitral valve is significantly higher than in the other positions This would be expected if the left atrial catheter tip was placed in the mainstream of the regurgitant flow

The standard deviation for all patients listed in table III 13 is 0 103 If cases CL 6191 and CL 7543 are omitted from the calculations SD is 0 069 Considering this SD another cas attract attention as its SD (0 21) is more than the general SD Case CL 8591 In this ca e the differences between RFLVO values are so high that it i impossible to declare which val e is the correct one A possible explanation, however is that th catheter tip in situation A was in or n ar pul monary vein and th t the high RFLVO of situation D is due to the catheter tip hav ing moved close to the mitral ostium For cases having a mean RFVLO bel w 0 10 the SD is 0 03 If 0 10 ≤ RFLVO < 0 50 the SD is 0 08 (excluding case CL 7543) If RFLVO is higher than 0 50 the SD is 0 09 (excluding case CL 6191)

Sinclair et al (1960) reported their experience in an experimental study Mitral regurgitation wa produced in dogs by "tying chordae tendineae or by pro duc ng a hole in a cusp Mitral egurgit tion was examined by ingle bolus dye dilution technique sing injection into the left atrium and sampling at 5 diff rent sites in the left tri m The a e ge vari tion from the mean wa 6 5 p r cent. In r gions des gnated s ephalad typical values were recorded in 6 of 11 ani mals Most of th t pical v l e were lower than those obtained el ewher The authors sugg sted that the low val es resulted from the sampling of und ed blood from the p lmon ry eins Elsewhere n the atri m po iti n near th val e neo th septum nd dor all val fo fr ctional regurgitation agreed with one anoth r Th most p ct c bl po ti n wa fo nd to be that close to th valv Th examinati b Sincl r et al (1960) thu g ee with the fi dings in thi study a the e thor lso e p rienced erroneou l low v lues in certain pos tion of the mpl g th ter Th i recomn ndation of pl cing the catheter close to the mitral osti m w uld howeve s seen from thi study result in erroneousl high alu in some p t nt

M rch t al (1967) d c bed p eviousl determined mitral r gurgit tion by infu ing dios t enon ntinuou l nto the left entricle nd sampling from the left trium The p tien s we am ned f r i complet mixing b with d wing th left t l c thet 5 8 cm in 12 tudi The ver ge difference in regurgitant fr cti n d t rm nat o wa 0 07 with ng f m 0 00 t 0 0

The concl i n f th tud well s f other that ampl ng t c rt in ite in th left trium m g e erroneously low or h gh val e f r gurgitant

f action (RFLVO) in single ca   As it is necessary in clinical pr ctice to have not only a statistically reliable method but also a method that   reliabl for each individual patient, I will agree with Sinclair et al (1960) n their recommendation that two sampling site should be u ed Th rror of low valu d e t sampling from the left atrium could probably be reduced through the u of a small thet passed through the l ft atrial sampling cathete   If this small cath t is advanc ed and pas   out into the lung field, the tip of th left atrial ampling theter must b within cl se to pulmonary v in. (This method wa used only in a f w of the l st c ses examined in thi study) Injection of contrast through th l ft atr al c theter in orde to outline electi ely a pulmonary vein would probably also be ble to reduce this rror (thi has not been xamined in this study) Th rror of high regurgitant fracti n (RFLVO) can be reduced if ttempt are m de to av id pla ing the left atrial c theter tip close t th m tral ostium

EVALUATION OF THE ERROR DUE TO THE SITE OF INFUSION INTO THE LEFT VENTRICLE

Th left ventricular vity can b subdivided int th areas: The outflow area (sub rtic are   ortic v stibul) th inflow   (mitral area) and the r maining part which will b d scribed he   th fund of th l ft ventricle

During th examination th position of th tip f th nfusion thet w s e amined by fluo oscopy nd regist red cording to th sch mati positions of fig III 3 A angiocardiogr phy w not used d ring th se examinations, the re g stration f th nf si n thet tip positi ns w only approxim tely exact. The loc ti n of th outflow are w   val ted from th ou e of th infusi n athet r nd on the inf rm tion from th   th t   ti n procedure s to whe the chang in diastolic p sure occurred n dvancing th nfusion atheter The locati n f th nflow ar w b sed upon th loc tion f th l ft trial theter- in addi t on, th mitral stium had ft n bee c thet rized by the l ft atrial cathet r Id ally a numbe of th t tip po itions in th l ft ventricular cavity should hav bee studied. H wev wh n th inf si n c thet w introduced int the l ft v ntricl p m tu b ts ft occurred th ec ssitated att mpt to find p siti n wh   no p m ture be t occurred. Thu th fundu of th l ft ven tri l ft rev aled nly ne positi n which w suitabl fo infusi n no pr m ture be t occurred. Thi xaminati ha acc rdingly been l mited to compar ng regurgitant f cti ns in th abov m nti ned three subdivisions of th left ven tricular vity

Th ctual procedur ons sted f placing th inf si n cathet i the fundu f th l ft v ntr cl following positi ning of th l ft atrial cath t s described ear l   B retra ting th l ft trial thet but leaving th infusion c thet in pl c th infl nce f th thet position in th left atrium w xamined s de- scribed bove Th l ft trial thet r w finally l ft in one position and the in

fusion catheter retracted to the inflow area and later to the outflow area. It was not possible to compare different positions in the fundus as too little space was left for manoeuvering; thus only the more extreme positions of the infusion catheter were compared.

Table III 15 Regurgitant fraction at different positions of the infusion catheter tip

C N	Sit f inf sion th t tip	Reg git nt f tio (RFLVO) Fund	I flow r	Outfl w a a	SD
3645		-	0 26	0 14	0 08
8314		-	- 0 01	- 0 02	0 01
7815		0 14		0 14	0 00
5068		0 02	-	0 07	0 04
5837		0 48	-	0 32	0 10
8560		0 17	0 22	0 33	0 08
5061		0 73	0 67	-	0 04
8591		0 24	0 71	0 06	0 33
7664		0 03		0 05	0 01
4465		0 14	0 25	0 13	0 06
4253		0 03		0 09 - 0 15	0 06
5226		0 06		0 02	0 03

A seen from table III 15 the number of patient examined I small only twel It is furth rmo e noticed that it was difficult to define the outflow area a in two cas s th regurgitant fraction increa ed when the infusion catheter wa retracted to the supposed outflow are although the opposite should ha e been expected (case CL 8560 and CL 4253) accordingly the last position in c se CL 4 53 must be regarded as belonging to the infl w area The SD for regurgitant fraction determinati n (RFLVO) (comp ring different injection sites) wa 0 13 f r all 12 c es If c e CL 8591 s om tted the SD is 0 04 All of th 12 cases x cept ca CL 8591 and ca e CL 5837 h d SD of RFLVO dete m nation of twice 0 04 or le

In five c the inf n cathet r was retracted from the f nd s to th inflow are (case CL 8560 CL 5061 CL 8591 CL 4465 and CL 4253) In three of these ca s a signifi ant increa n regu gitant fraction occurred (0 1 – 0 33 0 4 – 0 71 0 14 – 0 5 r specti ely) In case CL 4 53 a le signific nt in crea e w noti ed.

From these cases it must be concluded that a significant erro may occur in the determination of the regurgitant fraction (RFLVO) if the infusion atheter is placed close to th mitral valve

The effect of retracting th infusion catheter to the outflow area was examined in even case (case CL 7815 CL 5068 CL 5837 CL 8591 CL 7664 CL 4465 and CL 5226) In one case (c se CL 8591) a significant reduction in regurgitant fraction (0 24 – 0 06) w noti ed Reducti n in regurgitant fracti n (0 48 – 0 32) was noticed in case CL 5837 In two cases retraction w only performed from the inflow area to the outflow area. In on case (c se CL 3645) noti e ble reduction occurred in regurgitant fracti n (0 26 – 0 14) in the remaining case no change occurred (0 01 – 0 02) but th patient did not have any mitral egur gitation. From these c t must be oncl ded that a gnif ant err r in regu gitant fracti determinati n m y occu if th inf sion th t r tip is pla ed in the outflow area.

Few examinati ns h ve b en pe formed to determine the importance of the sit of injection. Sinclair et al. (1960) hav examined this in th ir experimental animal study already discussed (single bolu injection left atrial sampling dye dilution) They used the following sit of injection. *inflow region, outflow region,* mid-cavity apex. The result was th t in a total of 32 singl d t rminations th average variati n from the particular mean f individual animals was 2 7 per ent" (RFLVO of 0 027) Th nly gr t vari tion occurred when an injection apparently' was made through th mitral valve directly into the left atrium producing egurgitant f action approaching 100 per ent Th y ccordingly concluded that the site of injection was not important. Th discrepancy betw en th finding f Sinclair et al (1960) and th of the present study can probably be explained by diff renc s in th method f examination. Sinclai et al. (1960) used Rodriguez cathete No 5 with sp y tip and bol s i jection, wh reas n the pre nt study a slow ntinuous jection was mad through a Lehman the te No 4 7 ha ing only an nd hole thu if Sinclair et al (1960) had their thet in th outfl w are (r inflow regi n) th jet of the injection might reach further to the apex than using th p sent slow injection o it might be injected through th mitral stium apparently happened once in their study In addition, Sinclair et al (1960) ed dog in their study where s human beings were used *in th present study the p acti al differenc regarding th effect of injection site* s that th h art in thi study are likely to h ve been consid ably larger thus m king th distan e b twee the thre main injection sit considerably greater In additi n, in thi study extrem positions were studied intensio ally

Th t m st b maintained that th inf sion theter tip should not be placed in the outflow are in the vicinity of th mitral valve th mportanc of this tat ment i best ill str ted by se CL 8591 wh re very different regurgitant fractions w obtained u ing injections in th fundu inflow are and outflow area (0 24 0 71 0 06 espectively) It is possible that the erro of injection into unsuitable ar as, particularly th inflow area, could be reduced through the

use of a "pigtail" c theter with side holes at the outer curvature of the pig tail This however has not been examined in the present study

COMPLICATIONS

Determination of mitral regurgitation was attempted in 77 cases. In 28 cases (30 attempts) complic tion occurred necessitating termination of the examina tion. These complications are listed in table III 16 Some of these might appear trivial but it should be remembered that in all examinations the time factor was important if minor but time consuming complication occurred the prolongation of the examination would exhaust the patient and thus cause termination of the ex mination. Accordi gly with this experienc once a time consuming compli cation w met the examination was terminated at an early stage anticipating exha stion.

Trans septal left trial catheterization was the technically most difficult part of the examination due to th nlarged left atri m bulging into the right atrium As a m tt r of p inciple no puncture w attempted unles a stable position was obtained on palpation of the atrial septal wall In cases having a bulging left trium the needl oft n had to be almost straighte ed out in order to obtain a table position in such c es the site of puncture usually wa located rather low Although exp ience gained d g these exami ations made atrial septal puncture a ier t often wa d ff cult and t me-consuming procedure P ncture of the trial w ll occ r ed o 4 occ s 3 tim to the pericardial cavity once to the rta In 3 c ses wh r only th thin needle had been u ed f r puncture nothing occurred In n e the thick n edle also p ed through the atrial wall In thi e (which h s been rep rted elsewh e Lyngborg et al (1968)) pericardial t mponad g d ally dev loped the peri ard um was dr ined and the p tient re ov red neventf lly Increased resi tance on attempt to introduce the thick edl nd cathete w s met in 4 case a this could be due to an unusuall thick t al septum or n trial th ombus th xamination was terminated in these e In c the right trium could not be catheter ed by the needle or th peci l thet r ed for thi aminat on This wa p bably d e to abnormali ti th our f the c a in one of the c s the p tie t had been sub jected to m j bd minal su g r with dhesion a compli ation In 2 cases the c th t could not be manipul ted fr m pulmonary vein to the left atri m It w l t l m th t thi ould b due to oft catheter which did not maintain its original rv t

Fewer compl c t o w met b retrograde left vent icul r catheteri ation. The most eriou w stol which occ rred in one c and probabl wa an extreme vaso- agal re cti t p ncture f the femo al artery The p ti nt w s rapidly r suscit ted by f w blow n the che t and did not h any sequelae from the examination. This type of c mpli tion could probably be avoid d by

Tabl III 16 Complications uaing terminati n of examination.

T an pt l l ft t i l th t i ti n		14
At i l w ll pun t	4	
P n tu n t p ibl d t i t n	4	
Ma ip l tion f th t r f m p lmon ry v in t l ft t ium n t p ibl	2	
P in pu t	1	
St bl p itl n f n dl m bt in bl	1	
E try f n dl th t i t ight t i m imp ibl	2	
R t g d l ft ve t i l th i ti n		8
Asy l t t i l pun	1	
Bl di g t pun t it	1	
Cl tting f th t	1	
C pt f g id by S ldi g dl	1	
R p t d un f l tt mp t i l th t i ti n	2	
Hyp t n i n tt mp t LV th i ti n	1	
F il f LV th i i	1	
Righ h t th i i		1
Hyp t n i		3
E h i		2
R pid i l fib ill i		1
T h i l f l		1
		30

p medi ati n with tropi Som of th oth r compli tion could po ibly h bee vo ded if th disposabl Seldinge needl now ed had been vailabl th y are unif rml sharp

Right h art cath teriz ti n w unsucce sful in one e no superf cial bital vein w re visibl and deep vein w thrombosed. With experience the patient were routinely examined f superf cial veins If no suitable vena medi

na cubiti was found the patient was only catheterized from the femoral vein. In 3 cases hypotension caused termination of the examination; in 2 cases the hypotension was due to vaso-vagal attack (and exhaustion) in the remaining case pyrogen reaction was the cause of the hypotension. The technical error was due to a 3 way stopcock connecting the infusion pump with the infusion catheter being left closed as the infusion pump wa started the infusion syringe broke without any damage to persons

Table 17 Complications in patients not necessitating termination of examination.

F inti g due t p m tu b ts	1
At i l fib ill tion	1
H matoma in th g in	1
V s v g l ea ti n	6
Hyp t n i n	2

Table III 17 lists the complications which did not cause termination of th procedure The m st seriou one occurred in a patient who suddenly fainted due to runs of premature ventricular beat The infusion catheter was immediately pulled b ck to the a rta the p mature beats disappeared, and the patient regained consciousne s Th 2 ca es of hypotension were probably due to a p thidine injection, which was often given for discomfort in the back.

It is my impress n that determination of mitral regurgitation by the pr ent method annot be carried out in all patient neither an complications be completely avoided the number of unsuccessful xamination however can probably be significantly redu ed by using the principles outlined below

Th main diff culty s th trans eptal left atrial catheterization due to the often signif cantly enlarged l ft atrium protruding into the right atrium. The most important fact r in a suc essful trans eptal left heart catheteri ation is careful and thorough palpation of the interatrial septum in order t find the fossa ovali which s located more caudally and posteriorly in these p tients. In id ntifying the fo sa ovalis the feeling of the catheter tip slipping over the proximal border ("the limbic ledge) was onsidered a useful guide

Opacificati n of the left atrium by contrast injection into the pulmonary artery with the aim of obtaining a frozen videotape picture of the left atrium would probably be helpful as suggested by Gotzsche (1972) No attempt at atrial septal puncture should be performed unl ss th fossa ovalis can be identified and the needle is in stable position. A second important factor in trans septal atheteri

tion is that no attempts at passing the atrial septum by the thick needl and cathet should be mad unless a definite left atrial curv has b n obtained through trial puncture using the thin needle

The oth r main facto in obtaining successful examinati n is red ction in the duration of th examination to a minimum In orde t do this it would be of c n siderabl value if two physicians familiar with arterial catheterization took part in the examination, problem and c mplicati ns would th n be d alt with more rapidly and effectively and each examiner w uld be less tired during the examina ti n. In addition, s much preparation as possible should be d ne pri r t the examination. Procedur not definitely nec sary should be avoided; thu right heart c theteriz tion should be p rformed from th f moral vein, particularly if suitable vena mediana cub ti is not vailabl

Every effort should be m d to make the examination s comfortable possib l for the pati nt The pati nt should be well sed ted, but not ersed ted in order to avoid anxiety a well s hypotension, in selecting the dose f sedative the weight s well the psyche of th p tient should be tak n int onside tion. If narcotics h v to be given, tropine should be giv n simultaneously in order to avoid hypotension. Similarly tropine should b gi n prior to arte ial th t i tion in ord to avoid v so v gal ttacks

In this study the patients w re kept fasting from the ev ning p ior to the exam ination and during the e amin ti n, but in orde t void hypoglyc mia and also to m ke th p ti nts more comf rtabl I feel that they should be allowed soft drink te o ffee prior t and during the examination.

SUMMARY AND CONCLUSION

In thi chapt m thod f determinati n f mitral egurgitation ha been de sc ibed ing ontinuou infusion int the left ventri le of aline ntaining dio-ctiv krypton and ampling from th l ft atrium and from a syst mic art ry Suff nt curacy n th d t rminati n can be obtained provided that sample are tak n f om t least 2 cathete tip p siti in th l ft trium outsid the vi inity f th mitral o ti m (and the in agreement w th e ch other) provided that infu on do not oc in th inflow outflow area of th left ventricle and provided that 3 sampl from th left trium and th systemic artery are tak n f e h cathet tip po tion the l ft trium Th recircul ti n from the pul monary art ry t the pulmonary veins rep esents an error orrection f r which described Compli tions t the catheteriz ti n procedures involved in this m thod d occur th main problem being th t of th trial septal puncture due to the sually greatly enlarged left atrium bulging into the right atrium Recommen dation fo th prev tion of the e complication are described.

W th the po sible exception of angi graphic methods (sing left ventricular volum det rmination) the nly quantit tive method pre ently available for d ter

mination of mitral regurgitation demand injection of an indicator into the left ventricle and sampling from the left atrium and from a systemic artery Deter mination of mitral regurgitation using single bolus injection into the left ventricle carries the risk of poor mixing in the left ventricle as well as in the left atrium and is subject to inexactitude due to changes in stroke volume and heart cavity volumes a discussed earlier These errors are not present if continuous infusion of indic tor into the left ventricle is used except possibly the error due to varia tions in concentration within the left atrium and this error can be evaluated through sampling at different sites in the left atrium If a dye is used for continu ous infusion anoth r erro becomes more prominent. the recirculation of dye as discussed earlier The use of a radioactive gaseous isotope as indicator will re- duce this error provided that the blood/gas partition coefficient is low with conse- quent escape of radioactive gaseous isotope from the pulmonary circulation.

Two methods for determin tion of mitral regurgitation th ough the use of con tinuous infusion of a radioactive gaseous isotope have so far been described th t of Morch et al (1967) which ha been described earlier in this chapter and the present method

The method of Morch et al (1967) has the advantage of giving results at the sam time as the examination is carried out and recirculation is probably not of major importance provided that short intervals of infusion re used As in cardiac output determination by dye dilution, blood has to be withdrawn into a container (syringe) fo 1 te reinfu ion The present method does not give results at the time of the ex m n tion, but the r dioactivity count o n be performed convenient ly after the examination has been te min ted and rechecked without new catheteri z tion. The determination of mitral r gurgitation can be performed over longer tim intervals as the recircul ted krypton i determined thus allowing for e ami nation f change n mitral regurgitation secondary to exte nal factor (e g phar m ca) The decis on a to wh ch one of the two methods should be used will in each laboratory probably depend mainly on which r dioactive equipment a vail bl but also on the purpo of the investigation.

Chapter IV
Haemodynamic investigations

The h emodynami ffects of mitral gurgitation can b eval ted by animal perim nts or by th study f patients suffering from th di ease (and also in m chamical model) As a method, the study of patient b som shortcoming the main and theoretical on being that th pati nt xamined will arely be suff ring from mitral insuffici ncy alo e. Usually som time will h v elap ed b tw en the nset of mitral egu git tion and th examinati n. Th mitral insuff c ency m y thu be ccompanied by myocardial hanges such hypertrophy whil ther haemodynami nsequences m y be found su h h art failure nd increased pulmonary v scular resistance Myocardial di e not sed by mitral regurgi tation m y also b pre ent and m y be diffi ult t di gno and evalu t e g myocard al diseas du to h umati fev or nary arteriosel osis. Many p tient suffering from mitral regurgit tion will also h varying degrees f mitral stenosi

In ontrast to this situation, the examination in an animal exp riment s mo e cl an Th animal i suff ing from on disea nly In addition, it is usually techm ally po sibl t any tim to xamin gre t number of haemodynamic var able xperim ntally than clinically Furth rm va ou h emodynamic vari bl an be made to vary ccording to a particular experimental d sign.

EXPERIMENTAL INVESTIGATIONS

It i not the intenti n he to provid d tailed review of th h emodynamic onsequence of m tral gurgit tion found experimentally but to m ntion som inv stigations and findings which ar felt to be important. The article mentioned should b co sulted for m re detailed information.

V B sch (1892) examined mitral egurgit tion in an advanced xperim n tal model and mbined the r sult with hi clinical experi nc In hi opinion mitral egurgitati caused a decr se in systemi arterial p e sure well in peripheral venous p e sure an inc eas in pulmonary rtery p essure and hypertrophy f the ight ventri le H bs rved that the

lungs were "swollen" and "stiff" and concluded that this was due to an increase in left atrial pressure

In their animal experiments McCallum and McClure (1906) produced mitral regurgitation by means of a hook with which they cut only thin structures chordae tendineae and valves. The most striking change was that the left atrium was found distended with blood beating violently and synchronously with the ventricle. The pressure here became "markedly elevated showing great excursions" due to the contractions of the left ventricle. It was also found that the arterial pressure always sinks.

Straub (1917) using a cat heart lung preparation in his investigations observed dilatation of the left ventricle as a consequence of mitral regurgitation. Forward cardiac output was found to be only temporarily reduced.

In their classical studies Wiggers and Feil (1922) produced mitral regurgitation mechanically using a probe and plunger system. They found that mitral regurgitation occurred mainly in the ejection phase of the left ventricle. Pulmonary artery pressures were not changed by mitral regurgitation. If arterial resistance (was) increased in the systemic circuit, the regurgitation volume (increased) markedly at once

Barry (1927) found that mitral regurgitation caused a reduction in "forward" left ventricular output

Wegria et al (1957) found that mechanically introduced mitral regurgitation in the anesthetized dog caused an increase in myocardial oxygen consumption and coronary artery flow

In 1957 Braunwald et al. described an animal preparation with which a number of haemodynamic variables could be measured. Most important, however a left ventricular — left atrial one way shunt produced an artificial measurable mitral regurgitation. The findings using this preparation have recently been reviewed by Braunwald (1969) but will be mentioned here briefly

A degree of mitral regurgitation was produced twice as large as the dog's normal cardiac output. As a result, f rward flow decr a ed by approximately 25 per cent. Left atrial mean pressure increased from 5 to 11 cm H_2O (Braunwald et al 1957). In the same investigation increasing resistance to left ventricular ejection (afterload) caused significantly increased mitral regurgitation and left atrial mean pressure but decrea ed forward flow. It was also found that an increase in regurgitant flow caused a smaller elevation f left atrial pressure than a similar increase in f rward flow

Urchell et al (1968a) of the same group of investigators examined the haemodynamic mechanism further. The left ventricular pressure was found to reach its peak in early systole and then decline rapidly during ejection. Mitral regurgitation thus provided a low resistance outflow path in parallel with the systemic circuit causing a "striking" reduction in wall tension during ejection. With unchanged preload m tral regurgitation produced an increased total left ventricular strok volume and ejection fraction d spite an unchanged contractile state. An increased nternal energy transfer (acro s the series lastic element f Hill (1938)) w assumed to be the explanati n of this finding

Urchell et al (1968b) examined this furth r with the same model as before ex ept that a right ventricular bypas system wa lso used. In the first type of experim nts the f rward stroke volume was kept c nstant. Introduction of mitral regurgitation incr ased stroke volum 88 per cent and calculated contractile element work 38 per c nt. Despite thi there was only a modest increa e in myocardial oxygen consumption (14 per cent). In the second type of experiment the forward stroke volume was allowed to vary but the peak left ventricular pre sure was kept constant. M tral regurgitation caused an increase in total stroke volume of 97 per cent compared to control values with an incr a in calculated contractil elem nt work f 52 per cent. Despite this no increase occurred in myocardial oxygen consumption. In this experiment, however there was no increase in the calculated work per

f rmed by the contractile element in stretching the series elasti element whereas in th previous type of experiment th e was a 23 per ent increase Effectiv contractile element work, however increased markedly (46 p ent) Thus a pronounced increase in exc s stroke volume of mitral regurgitati n could be maintained at only a small added oxygen cost to the ventricl due to the low ene gy cost pe unit wo k expended in shortening, as opposed to that used for tension development

Parmley and Sonnenblick (1971) carried out an in vitro investigati n simulating mitral gurgitation by placing external springs in seri with ventricular c t papillary muscle A reduction wa ob erved in the rate of tension developm nt and developed tension. The potential erv of the Frank-Starling mechanism w reduced" as the syst m ope ated on the descending limb of th length tension curv at l wer r sting tension than normal

In th investigation d scribed above th immediate haemodynamic consequenc of experimental mitral regurgitation have been thoroughly studied, it appears that a significant degree of mitral r gurgitation i well tolerated in these sh rt tim experiments Th haemodynami mechanism in long term h art failure and deteri ation are howev not yet cl ar The ffect of mitral regurgitation on th haemodynamic nditi ns during exer i also emains to be examined.

HAEMODYNAMIC FINDINGS IN THIS STUDY

Th haemodynamic finding in th pre ent study will be described and discu sed in what follows. Th shortcoming of haemodynam inv stig tions in patients hav already been discussed in th beginning of this hapter Am ng other factor which may alter th haemodynam c condition tre tm nt with digitali and diur tic should be menti ned (Stampfer et al. 1968) a d scribed in chapter VIII, many of th patient in thi study rec ived su h treatm nt.

It should also be mentioned that ha modynamic conditio ar only described t rest; no exerc se studi w re made

METHODS

Th procedur of ath te ization was d scribed in the p eviou hapt r Thu right h art theterizati n w s perf rmed routinely prio to the tran eptal heart thet riz tion, th retrograd catheterizati n being p r formed subsequently and anmul ti n f the syst mic art ry f ampling b ing done l t

Pre sur m asurem nts wer mad using an electric capacitance manomet (' Hansen manomet [1]) (Hans n 1949)) The curve were observed by means of an scill scope (DISA Universal Indi t r[2]) S&W 4 channel oscilloscope type CE-4[1]) Th p sures wer rec rded with a photographic re c rd (Elem Klinik [3])) Elema inkjet recorder model 81 [3]) a "UV" Rec rd [4]) All the p essur w e rec rded with th midaxillary lin as ro referenc th p tient being sup ne M an pre sures were btained by opti al int gration.

Blood xygen wa m sured using th Brinkman haemoreflector[5]) (Zijlstra

1) Simon n & Weel, R akildev j 14 Albertslund, Denmark
2) DISA Electronic Hovedgad n 17 Herlev Denmark
3) El ma Schönander AB Solna, Sweden
4) SE Laborat ries, Feltham Middlesex, England
5) Kipp & Zonen, Delft, Holland

1958) The apparatus was calibrated on completely oxygenated blood The oxygen capacity was calculated by determination of the haemoglobin concen tration on a colorimeter (Haemotest[6]) This value in g per 100 ml was mul tiplied by 1 36 and the oxygen binding c pacity thus expressed in volume pe cent The actual oxygen content in the blood samples was calculated as the product of oxygen capacity and oxygen saturation. These values were correct ed for physically bound xygen (0 3 ml per 100 ml for arterial blood and 0 1 ml per 100 ml for v nous blood)

All patients were examined for the presence of intracardiac shunts by xamining the o ygen oncentr tion in the pulmonary artery and the caval veins Using a difference of 5 oxygen saturation per cent as criterion no shunts were ob erved. In some pati nts this examination had been performed prior to th examination for mitral valve disease and was thus not repeated.

Oxygen consumption was det rmined for 3-4 minutes by collecting the ex pired air in a Douglas bag The volume of the air was determined in a gaso-meter Th oxygen content in the air w s determ ned using the Haldane ap paratus

The metabolic rate was calculated by xpre sing the oxygen consumption in per cent of calcul ted oxygen consumption based on h ight age ex and we ght acc rding to the formula of Harr s and Benedict (1919) in the nomo gram of Astrup et al. (1959)

Cardiac o tput (forward fl w) w s calculated using th direct Fick principle (Fick 1870) nd expressed in lite s per minut per square meter surface The surfa e was cal ul ted from height nd weight using the f rmula of D Bois and Du Bois (1916) from th nomogram of Astrup et al. (1959)

For ch patient an aver ge RFLVO w s calculated u ing formula 2 of chapt r III As CLA CPV CSA etc an average of all th value obtained was sed prov ded that the infusion c theter was located optimally Values fr m one po tion (defined in h pter III) however w re not used under the f llowing circumstance

1 If the calcul ted RFLVO n that situation was gre te than 1 00
2 If the tip of the sampling c th t r was located l se to the mitral stium and sample from 3 positions of the atrial sampling c th te w re avail ble and th difference in RFLVO value between the situation in question nd the two lowest RFLVO val es was gre t r than the lim ts mentioned below in elation t the ave age RFLVO
   Av RFLVO ≤ 0 10 → RFLVO limit 0 10
   Av RFLVO betw en 0 10 and 0 50 → RFLVO limit 0 20
   Av RFLVO > 0 50 → RFLVO limit 0 30
3 If the trial mpl ng catheter w s p s bly clos to pulmonary vein and samples from 3 positi ns we v ilable and the RFLVO of one sampling positi n was le s than 0 10 and the diffe ence between the RFLVO of the position in questi n and th a erage of the two high st RFLVO val es was gre ter than the lim t mentioned bove nd r 2

A patient w s eliminated from the ha modynam c studies of thi chapter if the maximum differenc betwe n RFLVO in tw differ nt situati ns w s great than the above m ntioned limits provided that attempts h d been made at eliminating samples described above

The ave g RFLVO of a given patient btained s d scribed above will be u ed as th RFLVO value of that p tient in this and the following chapters

It wa my int ntion to have the examination pe f rmed under basal condi tion and th t th s me ondition should continue to be present througho t the examination. The xtent t which this intenti n w s sati fied an be valuated from the following Metaboli t was calcul ted in 35 cases the verage was 112 9 pe cent f the al ul ted normal value In 19 ase the ob erved oxyg n consumption w s within 90 115 p r ent of th alculated no mal

6) Testa L borat rium Marielundvej He lev D nmark

value In 3 cases it w s below 90 per cent of normal value (85 87 85 p r cent, respectively) in 10 case it was between 115 and 130 per cent and in the remaining 3 c t was 139 143 and 171 per ent, respectively Th high values of oxygen c nsumption w r probably d t nervousness and uneasine s this was in f ct present in 13 of 35 ses In one se the patient (MI No 12) who was psychop thi personality was fighting and biting the technician. The calculated oxygen c nsumption and cardiac output were not u ed in the case f th latte patient. As to the low valu s th se can ither be du to leakage of air or besity

The respiratory quotient (RQ) w xamined in 35 c ses. Th verag was 0 83 Th low st valu was 0 7 (9 se) th highest was 1 0 (4 as) and 1 2 (1 as) The l tt r as w ident cal with th above m nti ned pati nt (MI No 12)

An inv stig tion was und rtaken to see if som variabl changed during the procedure Sampl w e accordingly tak n f examination and pressur m sured befo e and after d t rmination f gurgitati n, s systolic left ven tricular p e sur w re not availabl for such ompar son, the peak rti p e sur (m sured bef re ent ring the left ventri l) was compared to th p ak l ft ventricular pre sure (m sured b f re th infusion cathete w s r tracted to the aorta)

Th esult of these mparisons are given in tabl IV 1 A statisti ally signifi ant difference w s f und regarding pulm nary oxyg n satur tion. As th syst mic art rial oxyg n saturation did not chang th r th xygen con sumption incr ed o the ardiac output dec ea ed. A th oxyg n onsump ti n was gene ally rath r high at the sam time th first sampl w taken (as described abov) th l tt po sibility m likely A po ible explana tion f this finding is th ti n of th edative given, such as ph obarbiton (which w given as routin) and pethidine gi en usually fo backpain (du to the prolonged supin positi n) S milarly th statistically signif ant d ea in peak left v ntricular pressure m st likely c used by th abov mentioned presumed decrea in ardi utput although dec e in syst mi v scular resistanc l an alt native explanati n, if th l tter w e th se thi could also hav been cau ed by edativ r pethidine

Th hang in spirat ry gas were small although in th as f pH and pCO_2 st tisti ally significant. Th id ba equilibrium change in th direction f cido s w thu statisti ally signifi ant, but minor Th chan g cannot b expected to influ nc th sult f the haemodynami am na tion.

MATERIAL

43 p ti nt ar ncluded in thi study Th se patient w re am g th 49 pa ti nt who w d sc ibed in hapter III Six pati nts were excluded from th 49 f th following reasons Th left v ntricl w not nt ed (MI 4) RFLVO d t rmination showed too large variation du t varying krypton nc ntr tion in th l ft atrium cc ding to th riteria d scribed un d Method (MI 34 and 47) pre sur curv were of unacceptabl qua lity f r mitral gradient det rmination (MI 10 and 26) c mpli ating heart val dise se w p sent (rtic inc mpetence in se MI 3) The 43 remain ing pati nt thu constitut th ba of this study Ag sex and oth charac t ristic f th se pati nt are described in chapte VIII

Am ng th 43 p ti nts optimal haemodynami studi could be perf rmed n 22 ses. In the remaining 21 ca som factor mad the RFLVO deter minati f the h modynami study l than optimal. Only one position of the l ft trial thet w sed in the RFLVO determination (se MI 5 6 7 8 9 12 17 and 19) th infusion athet position in the left ventricle w not known not loc ted t th fund (case MI 13 15 20 22 27 28 29 and 42) ardi output det rmination w pe f rmed (as MI 14 and 25) n rterio- v nou oxyge diffe enc w s m sured (case MI 1 2 and 18) It w hoped

in RFLVO values; on the other hand the average values are quite different in MIS group I MIS group II + III and MIS group IV + V

MIS group I includes the highest RFLVO values which are accordingly listed here: 0 87 0 87 0 86 0 84 0 83 0 81 0 75 0 69 0 68 0 63 0 63 0 59 0 57 (0 44) Thus in the cases with the highest values only a small fraction of the total output of the left ventricle will be used for forward cardiac output. MIS group V includes two cases with a negative RFLVO value of 0 02 and 0 01 respectively These values are theoretically in error and represent the vari tions in the method of regurgitant fraction determination.

The r sults described here may be compared to those of other authors who also determined the regurgitant fraction by injecti n or infusion of an indicator into the left ventricle with sampling in the left atrium and a systemic artery although the technique in other respects has been different.

Thus, Levinson et al (1961) using a single bolus dye dilution technique found a range of 0 00 to more than 1 00 among their 16 patients the upper limit was uncertain, however as great variations were seen on repeat determinations. Jose and Bernstein (1962) using single bolus dilution technique found a range of 0 07 0 79 (39 patients) Frank et al (1967) found an RFLVO range of 0 05 0 86 when they examined 19 patients; in 3 patients RFLVO was 0 75 or higher 0 75 0 78 0 86; the technique was continuous dye infusion. A range of 0 03 0 97 was reported by Günth r (1968) who used dye bolus injection in 25 patients; RFLVO values above 0 75 were found in two cases (0 78 0 97) Morch et al (1972) found an RFLVO range of 0 01 0 90 by exam ning 91 patients using conti nuous infusion of radioactive xenon. The range of RFLVO values described in the present study i thus s milar to that described by other autho s.

Regurgitant r ti (RRCO) s the r tio between regurgitant flow from the left ventricle to the left atrium and the forward c rdiac output, both flows measured in litr s per minute

This r tio s thu similar to the pulmonary/systemic flow r tio (PSFR) which is commonly used in evalu tion of congenital heart cas having n intracardiac shunt (the latter flow ratio (PSFR) is the ratio between pulmonary flow and systemic flow) A the pulmonary flow s dentic l with the shunt flow plus the systemic flow these two flow ratios are not immedi tely comparable If 1 0 is added to the egurgitant tio thi value is h emodynamically equival nt to the pulmonary/systemic flow atio Thus an RRCO valu of 1 0 is haemodynamically equivalent to a PSFR of 2 0

Table IV 3 shows th average and range of RRCO for e ch MIS group As expected from the cla sif cation into MIS groups a gr dual decrease in RRCO values occurred through the MIS group I – II III – V

High RRCO values w re found in group MIS I 6 6 6 6 5 9 5 4 9 4 2 3 1 2 2 2 0 1 7 1 7 1 4 1 3 (0 8) Th se values can be om pared to flow ratios in congenital intra ardiac shunts Thus in 27 patients who

T bl IV 2 Regu gitant f tion (RFLVO) i 5 MIS group

G p	A s	R s		
MIS I	0 72 (0 74)	0 87	0 44 (0 87 0 57)	14 (13)
MIS II	0 33	0 47	0 17	8
MIS III	0 24 (0 26)	0 48	0 12 (0 48 0 12)	7 (8)
MIS IV	0 05	0 09	0 03	5
MIS V	0 02	0 08	0 02	9

Th numb in p e th si indi t th esult f m ving case MI 1 from MIS group I to III,

Tabl IV 3 Regu git nt rati (RRCO) n 5 group

G p	A s	R s		
MIS I	3 39 (3 59)	6 6	0 8 (1 3)	14 (13)
MIS II	0 32	0 9	0 2	8
MIS III	0 35	0 9	0 1	7 (8)
MIS IV	0 05	0 1	0 0	5
MIS V	0 02	0 1	0 0	9

The numbers in parenthe i indicate the result of mov g case MI 1 from MIS group I t III

had only a ventricular septal defect with a left to right shunt giving a PSFR of 2 0 or more the PSFR was on an average 2 82 the 3 highest values were 6 2 4 9 4 2 and the lowest 2 0 (Sandøe 1963) Similarly Davidsen (1960) examined 57 patients who had an atrial septal defect which gave a PSFR of 2 0 or more (no right to left shunt was present); in these patients the average PSFR was 2 9; the 3 highest PSFR values were 6 0 5 8 5 2 and the lowest 2 0 The high regurgitant flow ratios described in the present study of mitral regurgitation are thus similar to the high pulmonary to systemic flow ratios described

Cardiac index (CI) is the forward' cardiac output corrected for body surface and thus expressed in litres per minute per square metre Table IV-4 lists the average and range for each MIS group As Wade and Bishop (1962) found the CI to lie normally between 2 5 and 4 5 $l/min/m^2$ and values below 2 0 or above 5 0 were definitely normal the number of patients within each group who have CI below 2 0 and 2 5 $l/min/m^2$ respectively is also listed It is seen that the cardiac index was low in each group except for group MIS IV which was also a selected group having both the smallest degree of mitral regurgitation and the smallest degree of mitral stenosis. As CI has been criticized as an index of cardiac output (Smulyan et al 1966 Burch and Giles 1971) cardiac output is listed in table IV 6 uncorrected for the body surface area

Other authors have described a decreased cardiac index in patients suffering from mitral regurgitation: Ross et al 1958 Bentivoglio et al. 1961 Miller et al. 1965 Günther 1968 It is also seen from these studies that the cardiac index was not below normal value in all patients It can thus be concluded from the present study as well as from those listed here that the cardiac index is often but not invariably below normal value in patients suffering from mitral regurgitation. Stampfer et al (1968) however described reduction in cardiac output during diuretic treatment; as described in chapter VIII a number of patients in this study were treated by diuretics.

Comparing the MIS groups no difference was seen between group MIS I and MIS II (p 0 69); however a statistically significant difference was found between group MIS II and MIS IV (p 0 02) but the latter group is quite small I accordingly do not find it convincingly proven that a definite correl tion exists in this study between the degree of mitral regurgitation and the cardiac ind x. This may appear surprising, but it should be r membered that this is a clinical study with all the limitations a described previously in this chapter It should also be mentioned that treatment does influence the ha modynamic variables as described earlier

Left ventricular index (LVI) is the total output of the left ventricle expressed in litres per minut per square m tre In table IV 5 LVI is listed according to MIS groups Table IV 6 shows the total left ventricular output uncorrected for body surface rea (LVO) LVI s alculated from the formul

Tabl IV 4 C rdi index (CI) acc ding t MIS groups,

G P	Cardia index (CI) A s	R s	n CI< 2 0	n CI< 2 5	n 11
MIS I	2 06	3 1 1 3	4	7	9
MIS II	2 12	2 8 1 9	3	5	6
MIS III	2 23	2 5 2 0	0	3	4
MIS IV	3 11	3 6 2 7	0	0	4
MIS V	2 41	3 9 1 9	3	5	8

Th cardi c index is forward cardiac output in litres/minute/square metre

Table IV 5 Left ventricular index (LVI) ording to MIS group

G P	L V I A s	R s	n LVI< 2 5	LVI> 5 0	n All
MIS I	7 95	16 1 5 3	0	9	9
MIS II	3 17	3 9 2 3	1	0	6
MIS III	2 76	2 9 2 6	0	0	4
MIS IV	3 23	3 7 2 8	0	0	4
MIS V	2 43	3 9 1 8	5	0	8

The left ventricular index is the total left ventricular output in litres/minut /square metre

$$LVI \quad \frac{1}{1-RFLVO} \times CI$$

LVO is calculated in a similar manner

In table IV 5 an obvious difference is seen between group MIS I and MIS II, which is not surprising, knowing the criteria for dividing the patients into groups. As seen from the table all the values in MIS group I are above the normal values described by Wade and Bishop (1962) The individual values of group MIS I are as follows: 16 1 10 8 10 2 9 8 8 3 8 1 5 6 5 3 5 3 $l/min/m^2$ LVI values as high as these have been found by other authors (Jose et al 1962 Frank et al 1967 Günther 1968) and are at the same level as seen for CI during exercise in normal human subject (Holmgren et al 1960) From the present and the previous studies it can be concluded that in severe mitral regurgitation the left ventricular output i significantly increased Consequently one would expect that these p tients had a limited possibility for increasing the left ventricular output during exercise

Regurgitant flow (RF) can be calculated from the formula

$$\frac{RFLVO}{1-RFLVO} \times CO$$

The r gurgitant flow within each MIS group is listed in table IV 6 As expected from the results from the LVI and LVO determinations the RF an reach high valu part cularly in MIS group I S milar high values have been described by Jose et al (1962) Frank et al (1967) Günther (1968) and Morch et al. (1972)

Stroke volume (SV) is calculated as total left ventricular output (LVO) divided by heart r te (HR) and i expressed in millilitre (ml) In tabl IV 6 it i listed for ach MIS group As expected an obviou difference in SV is een between group MIS I nd the remaining groups: this is not surpr sing, as RFLVO is an important factor in distribution into MIS groups as well as in calculation of SV

In group MIS I th f llowing SV value were found. 430 224 190 149 144 140 139 116 and 100 ml. The two highest values found in the article by Frank et al. (1967) were 341 and 236 ml respectively the two highest values by Günther (1968) w re 273 and 243 ml respectively th on value of 430 ml is thu higher than any oth r eported valu otherw se the results f SV determinati n by Frank et al (1967) and Günth r (1968) were imilar to those found in this study For comparison it should be mentioned that Holmgren et al (1960) in a group of healthy persons found esting stroke volum of 106 ml (ange 75 to 149 ml) and an exerc e value of 110 ml (range 85 to 137 ml) The stroke volum among patients with th most severe mitr l insuffic ency may thus be increas d above the upper normal esting and exercise value

Regarding the absolute values of flow in thi study t should be rem mbered that they have been al ul ted from two values not btained simultaneously: RFLVO and CO

Tabl IV 6 Cardiac output (CO) total left ventricular output (LVO) regurgitant flow (RF) nd strok vol me (SV) in different MIS groups,

G p	CO (1/ 1) A	CO (1/ 1) S	RF (1/ 1) A	RF (1/ 1) S	LVO (1/ 1) A	LVO (1/ 1) S	SV (ml) Av r g	SV (ml) S
	R	S	R	S	R	S	R	S
		3 38		11 28		14 66		181 1
MIS I	4 7	2 4 (9)	24 3	5 2 (9)	28 0	9 1 (9)	430	100 (9)
		3 38		1 70		5 08		70 2
MIS II	4 2	2 7 (6)	3 0	0 6 (6)	6 4	3 3 (6)	90	53 (6)
		3 98		0 92		4 89		68 9
MIS III	4 8	3 2 (4)	1 5	0 6 (4)	5 4	4 6 (4)	84	48 (4)
		5 23		0 21		5 44		71 4
MIS IV	6 4	4 4 (4)	0 3	0 1 (4)	6 7	4 7 (4)	83	56 (4)
		4 04		0 05		4 09		52 1
MIS V	6 3	2 9 (8)	0 2	0 1 (8)	6 2	2 9 (8)	86	35 (8)

The numbers in p renth i indicat the number of p tients examined

Table IV 7 Systemic artery oxygen saturation (SAOS) pulmonary artery oxyg n s turation (PAOS) arterio venous oxygen diffe ence (AVOD) and hemoglobin concentration (HB) in different MIS groups

G o p	SAOS (%) Av	SAOS (%) R	PAOS (%) Av	PAOS (%) R	AVOD (v 1 %) Av	AVOD (v 1 %) R	HB (g/100 ml) Av	HB (g/100 ml) R
MIS I	94 5	97 86 (2/14)	58 8	78 50 (8/12)	6 97	9 6 - 3 0 (10/12)	14 27	18 6 - 12 0 (13)
MIS II	94 1	98 89 (2/8)	60 8	74 50 (5/8)	6 36	8 6 4 3 (7/8)	13 58	15 7 - 12 0 (8)
MIS III	93 0	94 89 (3/7)	59 3	64 52 (5/6)	6 93	9 2 5 4 (6/6)	14 39	16 5 12 2 (7)
MIS IV	95 8	97 94 (0/5)	69 8	77 66 (0/5)	5 01	7 0 3 8 (2/5)	13 58	17 3 - 11 8 (5)
MIS V	94 2	97 90 (1/9)	64 6	74 57 (5/9)	5 60	8 3 3 9 (6/9)	13 39	16 3 11 1 (9)

Th numbe in parenthes indicate either number of patients having abnormal values/total number of patients or number of patients.

The systemic arterial oxygen saturation (per cent) (SAOS) is listed in table IV 7 It is seen that the oxyg n satur tion w s below 92 per cent in 8 of ... patients, the lowest value being 86 pe cent. No difference in arterial oxygen saturation was seen between the MIS groups

The pulmonary art rial oxyg n saturation (PAOS) in per cent of ... tur tion is also listed in table IV 7 Again no bvious diff renc was seen ... the MIS groups with the possibl exception of group MIS IV Using ... aturati n as the lowe normal val (Pedersen 1956) 23 out of 4.. patients ... decre sed PAOS which incid nce is similar to the incidence of patients ... a low cardiac index (20 out of 32 table IV-4)

Art rio-venou oxyg n differenc (AVOD) w measured in 40 pa... result is seen in table IV 7 Using the normal ange of 2 6 5 2 ... Pedersen (1956) a greater numbe of abnormal value were found ... index (CI) or pulmonary oxygen saturation (PAOS) but the distrib... mal values ccording to MIS-group wa not obviously different

Haemogl bin concentrati n (HB) wa measured in 42 p ti ... modynami examination and listed in table IV 7 ac ording to ... majo anemi wa present. The distribution of HB values ... does not app ar t be related to the degree f mitral regurgita... sis.

INTRACARDIAC PRESSURES AND RELATED VARIABLES

D stoli mitral gr dient (GRAD) th diff renc between ... trial p e re and th m an diastolic left ventricular pr ssure ... low both the m an p sure w re det rmi ed planimetr... e h defined as th p od betwee pre sur cro sov ... t the beginning of left ventri ular systol F each MIS ... the age and rang If c se MI 1 moved from group ... v ag will be 6 7 and 8 9 mm Hg, respectively The d ... gradient betwee group MIS IV and MIS V mainly deter... sed f distribution int MIS group More notew rthy is ... sured in som of the se of gr up MIS I, th following ... al 15 14 11 8 7 7 6 5 5 4 3 2 and 0 mm ... gradi nt w s 12 mm Hg) A n ti abl gr di nt in patie... m tral inc mp t nc h been d scribed by Nixon and ... with RFLVO f 0 50 m re (as in group MIS I) Gi... gr dient ranging from 12 t 2 mm Hg with an verag ... howev not surprising th t significant mitral valve ...

patients with severe mitral incompetence as the square root of the mitral gra dient is inversely proportional to the diastolic mitral valve flow according to the formula of Gorlin and Gorlin (1951) Thus if for a given valve area and forward cardiac output the gradient is 2 mm Hg it will increase to 8 if a mitral regurgi tation with an RFLVO of 0 50 is introduced.

Table IV 8 Diastolic mitral gradient (GRAD) and mitral valve area (MVA) in different MIS groups

	GRAD (mm Hg)			MVA (m^2)			
Gro p	Av r g	Ra g	n	Av r ge	Rang		
MIS I	7 1	15 - 0	14	6 7	12 2	3 6	8
MIS II	2 6	5 0	8	3 7	5 2	2 8	3
MIS III	8 4	11 - 6	7	1 7	1 9	1 4	4
MIS IV	2 6	4 - 0	5	3 3	4 4	2 7	4
MIS V	12 6	26 - 6	9	1 3	2 2	0 5	8

Mitral valve area (MVA) i here calculated ac ording to the formula of Go lin and Gorlin (1951) which also can be expressed as follows:

$$MVA \quad \frac{CO}{\sqrt{GRAD}} \times \frac{R\ R}{DIA} \times K$$

MVA is thus the inflow a e to the left ventr cl and xpressed in cm^2 CO is th cardi o output in litres per minut (without c rrection for surface area) R R the aver g R R interval and DIA the av rage duration of diastole (between pressure crossove s as described bove) K is a constant derived from the constant used in th formula f Go lin and Go lin (1951) but corrected for the use of litre and minute in CO thu in the place of th c nstant 31 of Gorlin and Gorlin (1951) 1 86 wa used. The use of this f rmula for d termination of mitral val area has been cr ticized from theo etical points f view (Rodrigo 1953 and Burger et al. 1956) but has none the less been used generally as t incorporates gr dient as well as cardiac output in the evaluation of valve orifice narrowing and most, but not all inv stigato s hav found good correlation to valve areas deter mined at surgery or autopsy (D kens et al. 1957 Abelman et al. 1958 Gustavson 1966) In the particularly careful study by Gustavson (1966) no statistically significant diff rence wa found between haemodynamically and surgically deter mined valve areas in p tients with sinus hythm (average value 1 83 cm^2 versus 1 67 cm^2) In patients with trial fibrillation, n correlation was found between

haemodynamic and surgi al estim t s ($p < 0$ 1 average 1 67 ve sus 1 04 cm^2)
F determination of the gradient Gustavson (1966) used th pulmonary wedge pressure and an assumed value for left ventricular diastoli pre sure s described in the original formula of Gorlin and Go lin (1951) It is thu possibl that th use of a simultaneously determined gradient in this study will reduc the rro of the stimate Cohen and Gorlin (1972) and Hammermeister et al (1973) hav ecently examined th riginal Gorlin and Gorlin (1951) formula f r a correction when using a direct gradient measurement. They found that the riginal nstant of 31 should b substituted by 37 9 (Cohen and Gorlin 1972) 40 (Hammerm 1 st et al. 1973) As th original c nstant of 31 has been u ed in the present study MVA likely to hav been over stimated by facto of 1 22 1 29 In thi study the Gorlin and Go lin (1951) f rmula was modified to take in count th re gurgitant flow

$$\text{MVA} \quad \frac{\text{LVO}}{\sqrt{\text{GRAD}}} \times \frac{\text{R R}}{\text{DIA}} \times \text{K} \quad \frac{\text{CO}}{\sqrt{\text{GRAD}}} \times \frac{\text{R R}}{\text{DIA}} \times \frac{1}{\text{1 RFLVO}} \times \text{K}$$

In thi onnection it should b remembered that CO GRAD and RFLVO w re not determined simultaneously thu introducing po sibl rr r

Table IV 8 lists th cal ulated valv areas found. A diff r nc between th valve areas exists between som group due to th criteria fo distribution into MIS groups Th valv areas f group MIS I are ather high. 12 2 11 1 7 1 5 5 5 2 4 4 4 0 3 8 cm^2 Günth (1968) found am ng 6 patients with RFLVO > 0 50 mitral valve ar s ranging from 10 0 to 3 7 m^2 with an av rag f 6 0 cm^2 Th valv areas found in the p ent study thu ar in agreement with those found by Günther (1968)

Th v wav in th l ft atrial pre sure rve ha be n subject fo study and discu si n, s t ha been sugg sted that the height and shap of th v wav would be indi tiv f th d gree f mitral gurgitati n (Lag rlöf and W kö 1949 V nn r and Holling 1953 Owen and Wood 1955 Ped sen 1956 M rrow et al. 1957 Connolly and Wood 1957 Ro et al. 1958 Marshall et al 1958 Neustadt and Shaff r 1959 Ham et al. 1959 Nix n 1961 Fairley 1961 Leach t al. 1962 Br unwald and Av 1963 Harmjanz et al 1966 Gould and Lyon 1967) Tabl IV 9 list variabl elated t the v waves: LAVP (l ft trial v wav peak pressure) WVP (peak f l ft tr al v w v in the pulm nary artery wedge tra cing) LAVP LVEDP (LAVP minu l ft v ntr cular nd di stolic p sur) LAVP LAMDP (LAVP minu left trial mean diastolic p ssur) LAVP/AOPP (th ti betwee LAVP nd rtic peak pre sure) and LAVP/LVMD (th tio between LAVP and l ft ventricular mean diastolic p e sure) It is seen that the v rag value grad ally decrease through group MIS I — MIS II + III — MIS IV but it also seen that onside abl ov lapping is pre ent between th group P rti ularly examined was whether any statistically signifi ant diff renc was present between the following MIS groups with egard to LAVP and LAVP LVED

Table IV 9 Variables related to the left trial v wave listed acc rding to MIS groups,

Gr ps		LAVP	WVP	LAVP LVEDP	LAVP LAMDP	LAVP/ AOPP	LAVP/ LVMDP	LAVAR	LAVDR
MIS I A		34 5	37 7	28 9	20 2	0 346	12 3	142 9	428 8
R ng		69–10 (14)	62 4 (10)	52–9 (14)	45–6 (13)	0 68–0 09 (13)	53–0 (13)	270–21 (13)	910–35 (13)
MIS II A		22 9	29 5	14 3	12 0	0 211	3 0	66 0	348 3
R g		57–8 (7)	53–11 (4)	36–10 (7)	36–1 (7)	0 49–0 08 (7)	5 1 (7)	125–29 (6)	555–110 (6)
MIS III Av		21 4	29 5	17 0	8 6	0 191	6 2	58 2	141 6
R g		34–9 (7)	44 15 (4)	23–7 (7)	13–1 (7)	0 30–0 09 (7)	13–5 (7)	136–11 (6)	240–75 (7)
MIS IV A		13 0	18 5	9 0	6 4	0 059	2 1	57 2	109 4
R g		38–6 (5)	26–12 (4)	23–3 (5)	23– 1 (5)	0 09–0 03 (4)	6–2 (5)	153–18 (5)	296–20 (5)
MIS V A		26 3	24 9	21 9	9 3	0 237	2 6	73 8	152 2
R g		33–15 (9)	37–18 (7)	37 10 (9)	13–3 (9)	0 39–0 12 (9)	9–0 (9)	131 28 (9)	305–57 (9)
Correl	R	0 15	0 29	0 12	0 25	0 26	0 27	0 35	0 47
t	p	0 35	0 14	0 47	0 11	0 11	0 09	0 03	0 002
RFLVO		42	29	41	41	40	42	39	40

All p essures are in mm Hg LAVAR and LAVDR in mm Hg/ ec LAVP left atrial v wave peak pressure WVP peak v wave p essure in wedge curve LVEDP left ventricular end di stolic pressure LAMDP left atrial mean diastolic pressure LVMDP left ventricular m an diastoli pre sure LAVAR rate of pressure ri e f left atrial v w ve LAVDR r t f p essur dec ase of left atrial v wave Th low r 3 lines indicat th result of a Spearman analy i of the correl ti n b tween RFLVO and th listed variabl R being th r el tion coeffi ient.

MIS I v MIS II, MIS II v MIS IV and MIS III v MIS V no such difference was found. *Braunwald et al. (1961) found that LAVP in normal persons was on the* average 12 8 with a range of 6 21 mm Hg The following numbers of patients within each MIS group had higher LAVP than 21 mm Hg- MIS I 9/14 MIS II 3/7 MIS III 4/7 MIS IV 1/5 MIS V 7/9 It is noteworthy that in the group with most severe mitral regurgitation, 5 out of 14 p tients did not hav a definit ly increased LAVP but in the group with most severe mitral stenosis a definitely increased LAVP occurred in 7 out of 9 pati nts. Each of the abov 6 variables wa examined for correlation to RFLVO using the Spearman test. A seen from table IV 9 no significant correlation was found and the correlation coeffic ent wa low On inspection of scatter plots having as abscissa RFLVO and as ordinate one of the above mentioned six variabl s, it was found that if a variable had reach ed a high val e the corresponding RFLVO would also b high in the majority of ases Thu if LAVP was 40 mm Hg o more 6 out of 7 patients had an RFLVO higher than 0 55 (fig IV 1) Similarly if LAVP LAMDP was 20 mm Hg or more

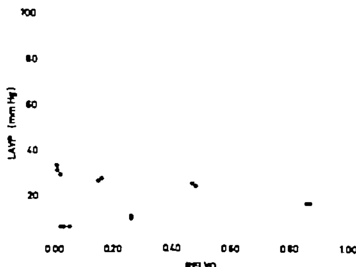


Fig IV 1 Left trial v wav peak pre sure (LAVP) in elation to regurgitant fractı n (RFLVO)

6 out f 8 patient had an RFLVO higher than 0 55 (fig IV 2) Similar results w re found f r WVP ≥ 40 mm Hg (7 out of 9 patients) LAVP LVEDP ≥ 30 mm Hg (6 out of 8 pati nts) LAVP/AOPP ≥ 0 40 (6 out of 8 patients) but not for LAVP/LVMDP In all th above mentioned 5 scatt r plots one patient devi ted from th rul that a high p essur variabl indi ted high RFLVO- case MI 46 this pa tient had an LAVP of 57 mm Hg and an RFLVO of 0 17 Thi patient, however w s the only known c e with the probabl diagnosi of papillary muscle dysfunc ti n econdary t myocardial infarction.

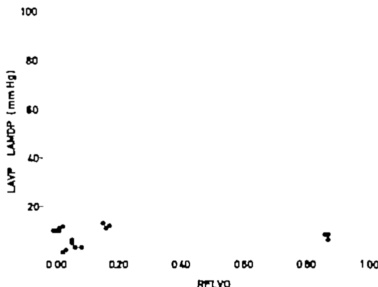


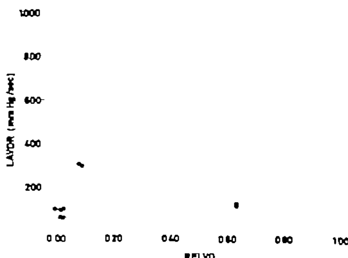
Fig IV 2 The differ nc between l ft atrial v wave peak pressure (LAVP) and left atrial mean diastolic pressure (LAMDP) in relation to egurgitant fr cti (RFLVO)

Thi p tient (case MI 46) sudd nly developed dyspno t the age of 56 years and 2 years prior to the determination of regurgitant fl w The dyspnoe in creased markedly and th patient w dmitted in severe left and right h art failure At auscultati n blowing holo systol murmur grade 2/6 wa found t the apex radiating to the axilla. The ele trocardiogram was remarkable in not showing any P w ve but the R R interval was constant. The QRS du tion w 0 13 ec with Q wave n II III and aVF leads Ch st roentgeno- gram showed an n r ed h art had w parti ularly f the l ft and with pulm nary stasi Right and l ft heart thet ization w s carried out incl d ing gurgitant flow determination. RFLVO w s found to be 0 17 LAVP 57 mm Hg LVEDP 30 mm Hg the pulmonary artery pressure wa 66/27 mm Hg th right atr al mean p essure 14 mm Hg nd the cardia index 1 9 l/min/m Two months later angioc rdiography with injection into th left v ntricl w s arried out showing signif ant m tral gu gitati n On month later th patient died sudd nly n her home autopsy w n t p rf rmed

It is poss ble that in th of papill ry muscle dysfun ti n the l ck f estric tion n m tral valve movem t may cause high V wave in the l ft tr al pre sure curv without giving rise to evere regurgitation. The othe c whi h did not always foll w the rule had p e sures at th l vel of the limits m ntioned In the group f m st eve e mitral egurgitation (MIS I) all the p ti nt (n 6) who had an LAVP of 40 mm Hg more w n imu hythm mo g th remaining 8 pa tients of that group (wh h d an LAVP of le than 40 mm Hg) sinus rhythm w s present in 4 patients

The shape of the v w ve in th l ft at al pr sure curv imilar t that of a t nt or mountain p ak nsisting of n scending d a descending limb P r ticularly the steepne of the d sc nding limb h be n elated to th degree of mitral regurgitation (Owen and Wood 1955) In the pr sent study line was dr wn

to fit the steepest part of the descending limb The slop of this line (LAVDR) was calculated in mm Hg per second. As seen from table IV 9 a differenc was noticed between the average pre sure in group MIS I v MIS II but LAVDR showed no statistically significant difference between the two groups ($p > 0\ 05$) A diff nce was also seen in the ave age LAVDR between group MIS II v MIS IV and th LAVDR valu s were almost statisti ally different (p 0 05) betw en the two groups No major difference was seen between the av rage value of groups MIS III v MIS V and no statistical diffe enc was een betwe n th LAVDR valu of these two groups Using Spearman s test a signif cant orrelati n was found between RFLVO and LAVDR but the c rrelation oefficient was low (table IV 9) An attempt t improv the correl tion by using LAVDR/LAVP as pr sure variabl did not result in any high r correlation coefficient (corr lati n coefficient 0 32 p 0 02) neithe was the correlation imp oved if LAVP × LAVDR w used as pressure v riable (rrelation coeffic nt 0 44 p 0 005) The fact that the correlation between a mplex pre sur variabl (containing LAVP s well LAVDR) and RFLVO w s not bett than using LAVDR al ne s probably relat d to the finding that LAVDR was significantly correl ted to LAVP ($p < 0\ 01$) although the orre l tion coefficient w s low (0 48) On a scatt plot using RFLVO as abscissa and LAVDR as ordinat 6 out of 9 patients with an LAVDR of 400 mm Hg/ ec r mo e also had an RFLVO of 0 35 more th excepti n t the rul w as p e viously ase MI 46 (fig IV 3)



F g IV 3 L ft tr al v w d scent rat (LAVDR) in elation to regurgitant fr ction (RFLVO)

U ing the slope of line fitting th ascending limb of the v wave LAVAR can be calculated like LAVDR and also in mm Hg/ ec From table IV 9 it i seen

increase in LVEDP and LVMDP usually indicates left ventricular failure but an isolated increase in LVEDP can be found in left ventricular hypertrophy (Hansen 1967) indicating decreased compliance of the left ventricular wall. As described earlier in this chapter the level of the LVEDP and LVMDP also depends on the medical treatment given. Regarding the pressure findings in this study it should be mentioned that patients who clinically were in severe left heart f ilure were not examined.

The left atrial m an diastolic p essure (LAMDP) was calculated by planimetry as was LVMDP The distribution of pressure values according to MIS groups is seen from table IV 10 As LAMDP in the patients of this study depends mainly on mitral valve gradient, it is not surprising that the highest average values were found in groups MIS I MIS III and MIS V

Left atrial wav peak pressu e (LAAP) could not be calculated in all patients a many p tient did not have sinu rhythm The numbers are thus small not allowing for any comparison between the MIS groups It is noticed that LAAP is abnormally high in 2 of the patients in groups MIS I using 12 mm Hg as the upper normal val e (B unwald et al 1961) LAAP however is like LAMDP dependent on the degree of mitral stenosis

Th left trial mean p es u e (LAMP) is th major factor determining the pr ssure in the pulmonary vein and th s the major f ctor responsible fo the development of pulmonary oedem or stasis According to Pedersen (1956) the upper normal level s 15 mm Hg From table IV 10 it is seen that no obvious d fferenc s were present among the MIS groups except for MIS group IV As this group consists of patients with a mall mitral regurgitation and/or a small mitral stenosis thi is not surpri ing Among the other group half or more of the patients had an increased left trial mean pressu e

Pulmonary art ry systolic (pe k) pre sure (PASP) pulmonary art ry diastolic pre sur (PADP) and pulmonary art ry mean pr ssu e (PAMP) re listed in table IV 11 Thi table also l st the number of p tients having abnormally high pressure using 35 11 and 19 mm Hg, r spectively the upper normal value (Pedersen 1956) Th s pulmonary hypertension was present in all the p ti nts having signif cant mitral stenosis (group MIS III and MIS V) and in the majority of tho e having significant m tral egu gitati n. PAMP s dependent on three variabl s the m an pressure in the pulmonary vein (which n rmally is n arly identical to LAMP) the cardiac output and the pulmonary vascular resi stance

The pulmonary v scular esistanc (PVR) was calculated s the difference b

Tabl IV 11 P sur m sur m t in th pulm nary artery and right at ium

G p	PASP	PADP	PAMP	PVR	RAMP
	A	A	A	A	A
	R S	R S	R S	R S	R S
	50 1	21 8	33 2	676	5 6
MIS I	107 13 (6/14)	46 6 (11/14)	72 8 (11/14)	1830 190 (7/10)	9 0 (3/12)
	35 9	15 3	24 4	441	5 6
MIS II	68 0 (4/8)	29 7 (3/8)	43 11 (5/8)	640 230 (5/6)	14 0 (3/8)
	49 5	26 3	35 1	323	4 6
MIS III	63 15 (5/6)	36 18 (6/6)	45 25 (7/7)	370 280 (2/2)	8 1 (1/7)
	30 4	13 4	20 6	232	3 8
MIS IV	38 17 (2/5)	20 6 (4/5)	29 13 (2/5)	360 150 (1/3)	9 1 (1/5)
	48 0	23 0	33 7	524	5 1
MIS V	77 30 (6/9)	36 16 (9/9)	53 24 (9/9)	1200 220 (6/7)	10 0 (3/9)

The pressure in mm Hg PVR i dyn sec $\times$ cm [5] p r square m tre body surfac PASP is pulmonary art ry systolic p e su PADP pulm nary rtery di st lic p essure PADP pulmonary rtery di st lic pro sure PAMP pulm ary artery m an pressure PVR pulmonary ecular resist nce RAMP right atrial m pre sure The number i p renthesi indicate the numb of patie t having abnormal values (as defined in t xt)/total number of p tients.

tween mean pulmonary artery pressure and mean wedge pressure multiplied by 80 and divided by the cardiac index. The unit is thus dyn. sec × cm $^{-5}$ per square metre The result is seen in table IV 11 Also listed is the total number of patients in each group with a PVR above 250 units and thus a significantly increased pulmonary vascular resistance No significant difference was proven between group MIS I v MIS II and group MIS II v MIS IV (p being 0 95 and 0 17 respectively) In the group of most severe mitral regurgitation (MIS I) the following values were found 1830 1820 1110 590 320 300 260 250 190 90 dyn. sec cm $^{-5}$ per m^2 Thus 3 patients had a severely increased PVR 3 patients a moderately increased PVR and 4 patients a normal PVR This wide range of PVR values is similar to the one described by Ross et al. (1958) and Bentivoglio et al (1961)

Right atrial mean pressure (RAMP) is listed in table IV 11 No obvious difference was seen between the MIS groups regarding average values with the possible exception of group MIS IV If an RAMP of more than 7 mm Hg wa used as a sign of definite right heart failure (Pedersen 1956) only 11 out of 41 patients were in right heart failure Bentivoglio et al. (1961) found a similar range among his 65 p tients suffering from advanced rheumatic mitral regurgitation

Table IV 12 lists the pressure in the ascending aorta No obvious difference is seen between the MIS groups again with the possible exception of the small group MIS IV The rather low values seen in some patients have been discussed earlier in this chapter

The systemic vascular resistanc is also listed in table IV 12 No definite differences between the MIS groups w re noticed

<u>In conclusion,</u> the haemodynamic findings in this study demonstrate that patients suffering from sev re mitral r gurgitation have a high total l ft ventricular output at the same level as seen in ventricular septal d fect and during ex r cise Severe mitral regurgitation i often, but not always followed by a reduction in forward cardiac output, but rarely by increased left ventricular diastolic pressure (many of the p tients in this study howev r were under medical tr atment with digoxin r diuretics) A ignificant mitral diastolic gradient is not incompatible with sev re mitral egurgitation. Incre sed pulmonary vascular resistance was commonly but not always found in severe mitral regurgitation.

The height and descent rat of the v wave of the left atrial pressure tr cing did not correlate well with the degree of mitral regurgitation. If these values were very high however significant mitral regurgit tion was found to be present; the latter observation w based on a small number of pati nts Other variables and combinations of variable were not found to be more helpful in evaluation of the degree of mitral regurgitation.

T bl IV 12 A rt pre sure m surements and syst mi v scular resistanc in diff rent MIS groups.

G p	AOSP A R S	AODP Av R S	AOMP A R S	SVR Av R S
	106 2	67 3	84 2	3341
MIS I	118 93 (13)	80 60 (12)	96 73 (9)	4500 2210 (6)
	113 8	68 1	82 4	2979
MIS II	168 75 (8)	85 54 (8)	85 54 (8)	4130 2020 (6)
	110 0	63 3	83 3	2736
MIS III	138 75 (7)	78 47 (7)	99 58 (7)	3320 2240 (4)
	124 0	75 3	92 0	2453
MIS IV	182 94 (4)	94 56 (4)	129 68 (5)	3290 1850 (4)
	116 8	68 9	86 1	2842
MIS V	155 84 (9)	99 50 (9)	109 65 (9)	3690 1520 (8)

Pressures are in mm Hg SVR in dyn. sec $\times$ cm ^{5} per square metre AOSP is a rtic (peak) systolic pressure AODP is aortic diastolic pressure AOMP i ortic mean pressure SVR is syst mic vascular resistanc SAOS systemic art rial oxygen saturati n. PAOS pulmonary xygen saturation. Th numbers in parenthesis are the numbers of patients xamined.

Chapter V

Roentgenological examinations

This chapter describes the findings in plain chest roentgenograms with the aim of examining their correlation to the degree of mitral regurgitation as well as to other haemodynamic findings.

As the heart as well as the individual heart chambers are 3 dimensional, evaluation of their size should be based on measurements in each dimension resulting in a determination of their volume. This principle has been used for more than 30 years in determination of the total heart volume. In evaluation of the individual heart chambers, however, this principle cannot be applied as these chambers can usually not be delineated in ordinary chest roentgenograms. An estimation of the size of an individual heart chamber can often be obtained by observing its contour (e.g. posterior or prominence of the left atrium indicating its enlargement); the impression of enlargement in different directions and dimensions can be combined into a total impression of the enlargement of the individual heart chamber. A further purpose of this chapter has accordingly been to examine which of these semiquantitative and more or less subjective 2 dimensional or total 3 dimensional estimates of individual heart chamber enlargement were of practical value in evaluation of patients suffering from mitral disease.

As measurements are preferable to semi subjective impressions, the aim has also been to evaluate whether some measurements, even 1 dimensional, could be used as indicators of individual heart chamber enlargement.

It has not been the aim of this chapter to evaluate the pathoanatomical and pathophysiological background for the abnormal roentgenological findings.

MATERIAL. Roentgenological examinations were performed in all patients. In one case (MI 31) however, the roentgen films had disappeared at the time of review. This study thus includes the 43 cases described in chapter IV except for one case, making a total of 42 cases available for examination. Age, sex, and other characteristics are found in chapter VIII.

MATHODS. The plain chest roentgenograms were taken in the erect position using in all patients the posteroanterior (P A) as well as the left lateral

(LL) projecti n. In 28 cases supplementary roentgenograms we taken in the l ft ante or oblique (LAO) and right anterio obliqu (RAO) projecti ns In th se 28 cases as well as in 5 additi nal c e pi ture were taken in LL projection while th p tients w re swallowing barium sulphat ontrast, in ord r to delineate th post rio bord r of the left atrium. Th film focu di tance was 2 m, g nerally 150 kilov lt and 320 milliampe w re u ed th milliampere sec nd (MAS) varying between 4 and 25

The roentgenogram which we used for evaluation in thi chapter we e taken during the admi sion for haemodynamic examination, as the app aranc f the heart and th lung f elds chang according to th linical onditi n and is influenced by the treatment (g by digoxin and diureti s) th roentgenogram we usually taken just a few day befor the haemodynamic examination.

Heart volume (CVI) was det rmined by the m thod f Rohr (1916) and Kahledorff (1932) modified by Jon ell (1939) and exp ssed in ml p m² body surf ce (th surf e area wa cal ul ted as d scribed in chapter IV) Th exposures w m de unrelated t th cardiac cycle

Enlargement of heart hamb r was evalu ted by observati n of th confi gurati n of th heart shadow in the different projections. A qualitative eval tion w s made as t whether enlargem nt was ab ent, qu stionably p sent, or definitely p sent. Th latter divisi n was usually subdivided into moderat pronounced and oc sionally v ry pronounced nlarg m nt.

Left v ntricle (LV) In th left lat ral projecti n (LL) emphasi was at tached to nlargem nt below th notch eparating the l ft trium and th left v ntricl if it wa visibl In the P A projection, no enlarg m nt, qu sion abl enlarg ment r definite nlargem nt wa noted depending on whether the low r l ft heart borde formed a straight line showed slight prominence or was d finitely prominent. In th LAO projection t was noted wheth n larg ment w s present or not. A total impressi n of l ft ventri ular enlargement wa obtained using all the available p oj ctions Finally it w noted wheth r the foll wing selected crit ria w re fulfilled· LV enlargem nt was ec rded as pres nt, if such w s een in th P A LAO p ojections; no en larg m nt was ecorded if no su h enlargement was seen in the LAO projection, in all other se qu stionabl enlargement w s recorded.

Attempts t quantitativ det rmination f LV enlargement w re made by the method of Hoffmann and Rigl r (1965) and Euler et al. (1959) In the f rm r method the sagittal distan betw en th posteri r spect of the inf ri r aval vein and th poster or shadow f th left ventricl u ed as an indic t r of LV nlargem nt. In th l tter method the following m asurem nt w re used: A (th h iz ntal distanc in th LL projection between th anterior pleura and the posteri p int f c ntact betw en th left h art and th l ft l af of th diaphragm) and B (th ho iz ntal d stanc betwe the ant ri r and post pleural su fac m asured at th am level A) in thi study th rati A/B was used, wher Eul et al. (1959) used B/A.

Left tri m (LA) A total impre sion f LA siz w btained through the u f all th point f evalu ti n mentioned below In th LL p ojection, n largem nt wa evalu ted by observing th post rior prominence of the heart shadow above th prev ou ly m nt oned notch; film taken during barium swallowing wer used in particular in thi valuation. Th P A projection w used f evaluating the promine f the left atrium b low the pulm nary arch. In th am projecti (P A) ttenti n w paid to th right heart bor d r th pre enc of doubl convex contour w u ed as sign of l ft atrial nlarg m nt. In th P A projecti n it was also noted whethe the left main bronchu was elevated. Separ t evaluatio of LA enlargement in th LAO and RAO p ojection w e not perf rmed.

A quantitati e evaluati n f LA enlargement was attempted in th P A projection by measuring th distance on a ho izontal line between the double con tour f the right heart border and th atrial prominence below th pulm nary arch. This m asur ment will be ef rred to as left atrial width (LAW)

Right v ntri l (RV) In the LL projection reduction of the space between th upp ant ri part f the heart shadow and th sternum was used as

sign of right ventricular enlargement. RV enlargement in the LAO projection was also evaluated A total impression of RV enlargement was obtained through the use of these two projections In addition, any elevation of the apex was evaluated in the P A projection.

No quantitative evaluation of RV enlargement was attempted.

Right atrium (RA) Enlargement of the RA was evaluated in the P A view by observing the prominence of the RA to the right. A quantitative evaluation of RA enlargement was attempted by measuring the maximum horizontal di stance between the right border of the RA and the midline ("right atrial width index" RAWI)

Calcification of the mitral valves

This was evaluated by the use of tomography in the RAO projection. Tomography in the LAO projection was also available in the majority of cases

Examinati n of the pulmonary artery

The P A projection was examined to determine whether the pulmonary arch was prominent or not In addition, the width of the descending branch of the right pulmonary artery was measured.

Pulmonary congestion and oedema

These conditions were evaluated through the following signs

Dilatation of the upper pulmonary veins, in contrast to the normal or relatively narrowed low r lung vessels (Ellis 1965)

Kerley B lines or septal lines: Short, sharp lines seen only at the bases usually less than an inch long and running transversely outwards to touch the pleural margin (Kerley 1951)

Kerley A lines: Lines several inches long rather ragged and radiating from the hilum. They do not bifurcate and they do not follow the normal branching pattern of bronchi and vessels (Kerley 1951)

Granular lung densities Granular pattern of increased density in the lung fields" (Ellis 1965)

Interlobar pleural exudat ,

Costo-phrenic pleural effusion (or basal pleural effusion) This was only examined in the LL projection and in the P A projection Thus, no pictures were taken in right or left decubitus.

Cloudy opacities were evaluated according to the description of J ckson (1951) "Dense cloudy opa ities covering both hilar regions often obscuring the details of the lung roots and of the adjacent lung structures. Th shadows spre d outwards from the hila over the central portions of the lung fields and down into the lung bases' The cloudiness usually ends before it reaches the chest wall Being usually bilateral the cloudiness often has a butterfly or bats wing appearance

The roentgenograms of the hest were reviewed retrospectively and consecutively The heart shadow was evaluated by the author alone whereas the lung fields w re evaluated by a senior radiologist (F Efsen) in collaboration w th the author

Electrokymography (J dg et al 1958) was not done Nor was fluoroscopy of the chest with the aim of evaluating systolic expansion of the left atrium as advocated by Brigden and Leatham (1953) For technical and practical reasons neither angiocardiography nor cineangiocardiography was performed.

RESULTS AND COMMENTS

HEART SHADOW

Cardiac volum index (CVI) i listed according to MIS groups (tabl V 1) Using th upp normal valu f r CVI of M ure et al (1955) which i 510 ml/m^2 f men and 440 ml/m^2 for w m n, 35 out of 40 p tients had enlarged h arts. It is seen that the rang of values i large within ach MIS group In all group except MIS IV the ave age CVI was onsiderably increased, the high st average valu is seen in group MIS III, which i th group of signif cant mitral stenosis and signi ficant mitral regurgitation; the small st averag valu is en in MIS group IV which is the group of minor mitral stenosi and minor mitral regurgitation. It noteworthy that the averag CVI was higher in group MIS III (which included pa tients having significant mitral stenosi as well as mitral gurgitation) than in group MIS I which i th group of dominant and ever mitral regurgitation. In th l tter group the foll wing CVI value wer found. 1680 1360 1250 1160 970 890 780 770 740 690 590 470 360 ml/m^2

Table V 1 Cardiac volume index (CVI) according to MIS groups

	CVI (ml/m^2)			
G p	Av g	K	s	(A)/ (T)
MIS I	900	1680	370	11/13
MIS II	740	900	420	7/8
MIS III	1127	1530	660	5/5
MIS IV	548	720	450	4/5
MIS V	701	1340	390	8/9

n (A) number f patients with abnormal values,
n (T) total number of patients

Only few report on the heart size in mitral regurgitation are available Sel and Katayama (1972) reported that in 61 patient who had mitral insufficiency

diagnosed by surgery th overall cardiac size as seen in P A view was en larged in all patients Gro s enlargement in 27 cases moderate enlargement in 27 cases and slight enlargement in 7 cases

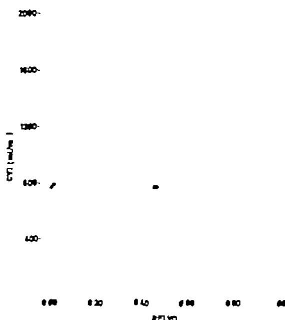


Fig V 1 Cardiac vol m index (CVI) in relation to regurgitant fraction (RFLVO)

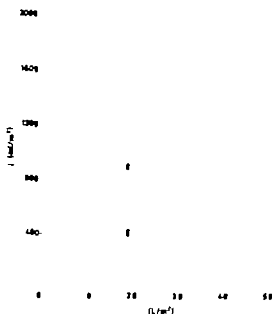


Fig V 2 Relationship between cardiac volume ind x (CVI) and cardiac index (CI)

Tabl V 2 C el tio b tw n roentg nologi al findings and the variabl s

	CVI			LAW		
	R	p		R	p	
RFLVO	0 33	0 04	40	0 26	0 20	27
CI	0 37	0 047	30			
LAMP	0 19	0 25	39	0 00	1 00	26
PASP	0 23	0 16	39			
RAMP	0 40	0 01	38			
GRAD				0 12	0 56	27
LAVP				0 00	0 94	26

RFLVO r gurgitant fr cti n, CI c rdi c index, LAMP left atrial mean pre sure PASP pulm nary rt ry systolic pressure RAMP right atrial mean pre sure GRAD diastolic mitral gradient LAVP l ft atrial v w peak pre sure CVI cardiac volume inde LAW left atrial width R correlation coefficient of Sp arman,

Table V 3 Left ventricular enlargement as seen in different projections and according to MIS groups

Group	Left ventricular enlargement at: LL proj 0	?	+	++	T	PA proj 0	?	+	++	T	LAO proj 0	?	+	++	T	Total impression 0	?	+	++	T	Selected criteria 0	?	+	T	Quantitative valuation according to: Hoffman and Rigler (1965) (cm) Av, range (n)	Euler et al (1959) (ratio) Av, range (n)
MIS I	1	7	4	1	13	3	2	8	0	13	0	4	3	2	9	1	4	5	2	12	0	5	8	13	1.78 2.8–0.8 (6)	0.52 0.4–0.6 (11)
MIS II	0	3	5	0	8	3	0	5	0	8	0	1	3	0	4	0	1	7	0	8	0	1	7	8	2.24 3.1–1.8 (5)	0.57 0.5–0.7 (8)
MIS III	0	4	3	0	7	3	1	3	0	7	0	1	1	1	3	0	5	2	0	7	0	3	4	7	2.05 2.1–2.0 (2)	0.53 0.4–0.6 (3)
MIS IV	0	4	1	0	5	3	2	0	0	5	2	2	0	0	4	1	3	1	0	5	0	5	0	5	1.70 1.8–1.6 (2)	0.48 0.5 (5)
MIS V	0	5	4	0	9	5	2	1	0	8	1	5	0	0	6	1	6	2	0	9	1	7	1	9	2.10 2.7–1.5 (2)	0.57 0.5–0.6 (3)
	1	23	17	1	42	17	7	17	0	41	3	13	9	3	28	3	19	17	2	41	1	21	20	42	(17)	(30)

T total number of patients 0 ? + ++ indicate degrees of left ventricular enlargement. For further explanation see text (methods)

As seen from table V 2 the question was examined whether the heart volum (CVI) was correlated to some haemodynamic variables. No high correlation coefficient were found, but a significant correlation to regurgitant fraction (RFLVO) (fig V 1) cardiac index (CI) (fig V 2) and right atrial mean pressure (RAMP) If the correlation between CVI and RFLVO only was examined in groups MIS I and MIS II (the groups of dominant and significant mitral regurgitation without signifi cant mitral regurgitation) th c rrelation coefficient did not increase (R 0 15) and the p value increased (p 0 52) It can be concluded accordingly that in p tients having mitral regurgitation, th degree of mitral regurgitation is only one f the factor det rmining the heart volum

Left ventricular enlargement. In table V 3 variou methods for evaluati n of left ventricular (LV) enlargement ar listed. In order to evaluat th se method the occurrence of LV enlargement in group MIS I can be compared to the occurrence in group MIS V LV enlargement would be expected to be common in the former group of evere and dominant mitral gurgitati n and rare in the latter group of dominant mitral stenosis. In group MIS I, LV nlargement w found in 5/13 8/13 and 5/9 p ti nts using the LL PA and LAO projections spectively In group MIS V LV ventricular enlargem nt w s found in 4/9 1/8 and 0/6 patient using the same projecti ns. In 1/13 3/13 and 0/9 patient of group MIS I no LV nlargement was found using th above m ntioned 3 projections, compared to 0/9 5/8 and 1/6 in group MIS V If all MIS groups ar val ted together qu stionable enlargement was found in 23/42 7/41 and 13/28 p ti nts respectively using the LL P A and LAO projections Th conclusion of thi omparison is o rdingly that in this study f patient with mitral valv disease left ventricular enlargem nt could not be satisfact rily evaluated in the left lateral (LL) projection, probably because the left atrium usually also nlarged in this disease The P A projecti n and th LAO appeared to be of similar value in evaluation of LV enlargement.

T bl V 3 also list the sults of evaluating LV enlarg ment using all available projections. Th same tabl shows the result of examin tion of th roentg nogram f LV enlarg m nt using th selected crit ria N obvious differenc i seen betw en the two method of evaluation.

Th method f quantit tive evaluation of LV enlarg ment w re not found of any valu se n from table V 3 Th inferi aval left ventricular distance f Hoffmann and Rigler (1965) w found t be mall in group MIS I than in group MIS V whereas th opposite would have bee xpected; simil rly the nve se rati f Eul et al. (1959) was smaller in group MIS I than in group MIS V whe the opposit would al hav been expected.

Using th total impression, l ft ntricular enlargement w s thus found in 7/12 patient having an RFLVO above 0 50 and in 9/15 p tients having an RFLVO between 0 10 and 0 51 Bentivoglio et al (1961) among 61 patients wh had "ad vanced" mitral regurgitation proven by operation or autopsy found left ventricular enlargem nt by roentgenologi al examination in 46 per cent. Storstein et al.

(1962) in a similar study of 30 patients found LV enlargement in 19 From these studies as well as the present it is thus apparent that LV enlargement is found in the majority of patients with significant mitral regurgitation, but not in all of these patients

Table V 4 Roentgenological evaluation of left atrial enlargement.

Gr p	T t l imp si (11 p j) n 0	?				T	L ft t ial width (m) R ng	Av	( )
MIS I	0	0	3	7	3	13	19 11	13 8	(10)
MIS II	0	0	2	5	1	8	15 10	12 8	(5)
MIS III	0	0	2	4	1	7	17 10	13 6	(5)
MIS IV	0	2	2	1	0	5	12 10	11 0	(2)
MIS V	0	0	2	5	2	9	16 9	12 2	(5)
T	0	2	11	22	7	42	19 9	13 1	(27)

T total number of p tients

Left atrial enlargement. Using the total impression in valuating left atrial enlarg ment all p tients except two we e found t have an enlarged l ft atrium (table V 4) In th group of dominant and severe mitral egurgitation 3 patients had a very enlarged left atrium 7 a considerably nlarged LA and 3 moderate enlargement. The distribution f left trial size was similar in othe MIS group except group MIS IV in which tw patient were found with questionabl enl rge ment of LA.

Bentivoglio et al (1961) found among his 61 case of advanced mitral regur gitation 2 8 12 52 18 and 7 per ent of hi p tie ts with 0 + ++ +++ ++++ +++++ degree of LA enlargement r spectively Simil rly M Gregor and Zion (1955) found among their p tients w th pred minant regu gitat on 15 62 and 23 per cent showing + ++ +++ degree f LA enl rgement respectively Left atrial

enlargement is thus found in most cases of severe mitral regurgitation but there is a wide range in size of the LA.

G aduation of left atrial size by measuring the l ft atrial width (LAW) orr lated well with th subjectiv graduation, but was only possible in 28 case due to difficulty in d fining the left atrial border (table V 5)

Using the l ft atrial width (LAW) a indication of left atrial size no correla ti n was found between thi variable and the degree of regurgitation (RFLVO) (table V 2) Between left atrial enlargement as d termined by th total imp es sion and left atrial mean pressure (LAMP) correl tion ($p < 0.05$) was found for + and ++ enlargement (table V 5) N correl tion, howev r could b found between LAW and LAMP (table V 2) In the group f slight l ft atrial enlarge ment (+) the left atrial v w ve (LAVP) was small r than in the group ++ nlarge ment (table V 5) but thi enlargement w not statisti ally signif ant ($p > 0.05$) Similarly no orrelation was found between LAW and LAVP (tabl V 2) H wever

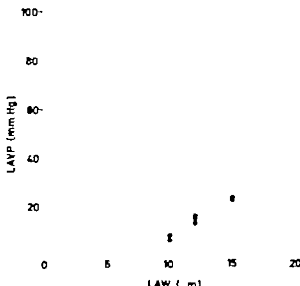


Fig V 3 Rel tionship betw n left trial v w ve peak pressure (LAVP) and l ft atrial w dth (LAW)

from sc tter plot having LAVP as abscissa and LAW as ordinate (fig. V 3) it een that all the p ti nts with an LAVP of m re than 40 mm Hg also had a re latively mall l ft atri m (LAW < 14 cm) The mitral diastolic gradient (GRAD) w found to b smaller in + LA enlargement than in ++ LA enlargement (table V 5) b t thi w not statisti ally significant ($p > 0.05$) no could a orrelation between LAW and GRAD be proven (tabl V 2) The ardiac index (CI) w s found

to decrease with increasing LA size (table V 5) but this correlation was not statistically significant (p > 0 05)

Table V 6 has been constructed to evaluate those factors of importance in en larging the LA in the group of severe mitral regurgitation (MIS I) as the group only includes 13 patients the individual values are given. It is seen that it is difficult to find a general explanation for the enlargement of the left atrium. How ever the small group of +++ enlargement is noteworthy as these patients all have large heart volumes (CVI) only moderately increased LAVP and atrial dys rhytmia the cardiac index was measured in only one of these patients and was found to be very low This group of patients is thus similar to the group of pa tients described by Braunwald and Ave (1963) although the left atrial pressures w re not normal, but moderately elevated. The group of patients also described by Braunwald and Ave (1963) as having high v waves (LAVP) did not appear to differ from the remaining patients regarding left atrial size (and heart volume) except that neither of these showed pronounced abnormality The degree of LA enlargement thus appears to depend not merely on one or two but on a number of factors

Right ventricular enlargement Table V 7 shows that it was considered easier to evaluate RV enlargement in the LAO project on than in the LL projection, as the occurrence of questionable enlargement was 4/28 in the former projection compared to 9/42 in the latter

Table V 7 also lists the incidence of elevated pex in the P A projection. Only one case of elevated apex was found This sign is thus of no use in evaluating RV enlargement in mitral patients

Using the total impression of RV enlargement this was found in 22 out of 42 patient (tabl V 7) In the group of severe and dominant mitral regurgitation (MIS I) 6 out of 13 patient w re found to have RV enlargement; among the pa tients of group MIS I who were examined in the LAO projection 6 out of 9 patients had RV enlargement. Bentivoglio et al (1961) who evaluated RV enlargement in the LL and right anterior oblique projection, found RV enlargement in 67 per cent of their patient with advanced m tral regurgitation. McGregor and Zion (1955) found RV enlargement in 69 pe cent in the group of predominant regurgi tation The f ndings on RV enlargement in this study are thus in agreement with th two studi s mentioned

Among th 6 patients who were not found to have RV enlargement the pulmo nary artery systolic pressure (PASP) was an average of 33 5 mm Hg in the group of 19 patients w th RV enlarg ment PASP was 42 8 mm Hg This differ ence w s not statistically ignificant (p > 0 05) but the number of p tients com pared was small.

R ght at ial enlarg ment w s evalu ted only in the P A projection (table V 7) This evaluation w s difficult questionable enlarg ment wa found in 32 out of 38 cases. The right atrial width index (RAWI) did not show any obvious dif ference in average values between the MIS groups except possibly for group

T ble V 7 Eval tion of enlargement f th ight v ntricle (RV) and right trium (RA) according to MIS groups

G p	Right t i l (LL p j) 0	?			T	l (LAO p j) 0	?		T	g me t T t l i p l 0	?			T	El vat d apex (P A p j) 0	?		T	RA enl rgement (P A pr j) 0	?			T	"Right t i l width i de (cm) R E	A ( )
MIS I	2	7	4	0	13	1	2	6	9	2	5	5	1	13	11	1	1	13	0	11	1	0	12	8 4	5 8 (12)
MIS II	1	5	2	0	8	0	1	5	6	1	0	7	0	8	8	0	0	8	0	6	0	0	6	7 4	5 2 (8)
MIS III	0	5	2	0	7	1	0	2	3	1	4	2	0	7	4	2	0	6	0	4	3	0	7	9 3	6 2 (7)
MIS IV	0	4	1	0	5	2	1	1	4	1	3	1	0	5	3	2	0	5	0	5	0	0	5	5 3	4 0 (4)
MIS V	0	8	1	0	9	1	0	5	6	1	2	4	2	9	5	4	0	9	0	6	2	0	8	8 4	5 6 (9)
T	3	29	10	0	42	5	4	19	28	6	14	19	3	42	31	9	1	41	0	32	6	0	38		

T total number of patients. For further explanation see text

MIS IV A significant correlation was found between RAWI and right atrial mean pressure (RAMP) and regurgitant fraction (RFLVO) ($p < 0.05$) but the correlation coefficient (R) was low (0 31 and 0 30 respectively)

Calcification of the mitral valves was found in 9 out of 41 cases the examination being inconclusive in 4 cases. The incidence of calcification was similar in the different groups from MIS I to MIS V: 3/12 1/8 2/7 1/5 and 2/9 Bentivoglio et al (1961) found calcification of the mitral valve using fluoroscopy in 33 per cent of their cases; this incidence is thus similar to that found in the present study

LUNG FIELDS

Prominenc of the pulmonary arch was not found in 32 out of 42 cases (table V 8) Definite prominence was found in 7 cases and marked prominence in an additional 3 cases. The low incidence of occurrence does not allow of any conclusion as to uneven distribution among the MIS groups The incidence of prominent pulmonary arch in group MIS I (3/13) is smaller than that found by McGregor and Zion (1955) in their group of predominant mitral regurgitation (47 per cent) and much smaller than in the examination by Bentivoglio et al. (1961) who found a normal pulmonary artery" examined in LL and right anterior projection in only 2 out of 65 cases. This marked differenc in incidence of pulmonary enlargement probably reflects mainly different criteria for this finding

The pulmonary artery systolic pre sure (PASP) was an average of 39 2 51 8 and 78 0 mm Hg, respectively in each of the three groups of prominence of the pulmonary arch as described in table V 8; these differ nces, however were not statistically different ($p > 0.05$)

Determination of the width of the d scending branch of the right pulmonary artery was possible only in 13 cases This number is too small for subdivision into MIS groups No correlation was found between thi measurement and the pulmonary artery systolic pressure (R 0 29 p 0 33)

For practical purposes pulmonary cong stion and pulmonary stasi are used a synonyms and evaluated by observ tion for the following signs, as described above

Dilatation of the upper pulmonary veins was found in 21 out of 39 cases. The left atrial mean pressure (LAMP) was an average of 19 1 mm Hg among the patients in whom this sign was positive (n 20 SD 7 9 mm Hg) compared to 12 8 mm Hg among the pati nts in whom no upper pulmonary vein dilatation was found (n 18 SD 6 6 mm Hg) This differ nc w statistically significant ($p < 0.01$)

Kerley B line were pres nt in 33 out of 42 cases. LAMP was 18 1 mm Hg in this group (SD 7 7 mm Hg) compared to 10 7 mm Hg in the remaining 8 p tients (SD 5 0 mm Hg) This differenc in average value was also statistically sig

Table V 8 Findings by ro ntg nol gi al examinations f th lung fields accordi g to MIS groups

C p	F al p lmo ry f h				Dil t ti f pp p lmo n y i			E rl y B li s pr t			G l r infilt ti n			B l pl al ex d t			Evid f p lm ry m stin		
	0/?			T	0/?		T	0/?		T	0/?		T	0/?		T	0/?		T
MIS I	10	2	1	13	7	5	12	2	11	13	12	1	13	9	4	13	2	11	13
MIS II	8	0	0	8	6	2	8	4	4	8	8	0	8	6	1	7	4	4	8
MIS III	3	3	1	7	1	5	6	2	5	7	5	2	7	4	2	6	1	6	7
MIS IV	5	0	0	5	3	2	5	1	4	5	5	0	5	5	0	5	1	4	5
MIS V	6	2	1	9	1	7	8	0	9	9	8	1	9	7	0	7	0	9	9
	32	7	3	42	18	21	39	9	33	42	38	4	42	31	7	38	8	34	42

T total numbe of p tients

nificant (p < 0 01)

Granular infiltrates were seen in only 4 out of 42 patients; all four patients also had Kerley B lines

Basal pleural exudate was found in 7 out of 38 p tients; all seven patients also had Kerley B lines

Among the patients who showed roentgenological signs of pulmonary congestion (as defined below) LAMP was 20 4 mm Hg for the patients with basal pleural exu date (n 7 SD 7 8) compared to 16 6 mm Hg in the patients without pleural exu date (n 24 SD 7 5) This difference was not statistically significant. Inter lobar pleural exudate was found in only 1 out of 41 cases Kerley A lin s were not found in any of 42 patients

Cloudy opacities were not found in any patients (this is due to a case selection, as no patients with signs of pulmonary oedema would have been subjected to this examination)

From the above mentioned findings and table V 8 it is apparent that Kerley B lines are the earliest signs of pulmonary congestion: only 20 out of 31 case with visible Kerley B line had dilated upper pulmonary veins whereas only one case among the 21 cases of upper pulmonary vein dilatation did not show Kerley B lines.

Thus using the presence of either Kerley B lines or dilatation of upper pulmonary veins as evidence f r pulmonary congestion, this was found in 34 out of 42 c ses (table V 8) No obvious difference was present between the MIS groups with regard to pulmonary congestion. In the group of severe and dominant mitral regurgitation (MIS I) 11 out of 13 patients had pulmonary stasis. Bentivoglio et al (1961) found pulmonary congestion in 59 per cent of their mitral regurgitation cases. In comp ring th incidence of pulmonary congestion it should be consider ed that this finding as described above is correlated to LAMP which again is related to the intensity of medical treatment as described in chapter IV

GENERAL CONCLUSION

The total heart volume (CVI) w s found to be signific ntly nlarged in the majority of p tient with severe mitral regurgitation, but mitral regurgitation was only one of the factor determining the size of the heart.

Enlargement of th left ventricle w found in slightly more than half of the cases with ignif ant mitral regurgitation; evaluation of the size of the l ft ven tricle as an isolated investig tion wa thus not found to b a reli ble guide in estimating the degr e of mitral regurgitation. Left ventricular enlargem nt could not be satisfactorily e alu ted in the left lat ral projection in these patients better results were obtained sing the P A projection and the LAO projection. The latter projection wa also found val able in estim ting right ventricular enlarge ment, and is accordingly recommended f r u e in combined mitral lesions

Left atrial nlargement was found in the overwh lming m jority of all the patients examined. The degree of left atrial nlargement depends on sev ral fac tors

Attempts to use 1-dim sional measurements as indi ators of individual h art chambe enlargement w unsucce sful for the left ventri le and qu stionably suc ssful for the right atrium but were found useful in th c e of th l ft atri m

Calcification of the mitral valves was found in less than 25 per nt. It wa not present more c mmonly in ases of mitral regurgitation than in cases of mitral stenosis

The pre ence of K rley B line w found to be the arli st sign of pulmonary congestion, with dilatati n of the uppe pulmonary veins as the second most sensi tiv finding A expected both these finding w re correlated t the left atrial mean pre sure

Chapter VI
Electrocardiographic examinations

This chapter describes and discusses the electrocardiographic findings in relation to the haemodynamic observations particularly regarding mitral regurgitation.

MATERIAL

This study includes the 43 patients who were described in chapter IV as having undergone a satisfactory haemodynamic examination. Age, sex and other characteristics of this material are to be found in chapter VIII

METHODS

All the electrocardiograms (ECGs) in this study were obtained with direct writing ink jet recorder*). 12 lead ECGs were obtained in all cases (I III aVL aVR aVF V_{1-6}) The paper speed during recording was 5 cm per sec

The terminology and abbreviations used in describing the electrocardiographic findings are those generally accepted S ... however deserve special remarks

Rhythm, In differentiating between atrial fibrillation and flutter the following rules were used If the atrial waves had an appearance similar to that of a P wave of normal height atrial flutter (AFL) was registered If no atrial wave was seen or the atrial waves was very small and the R R interval varying atrial fibrillation (AFI) was registered. If an atrial wave was seen but it did not clearly belong to either atrial flutter or fibrillation, atrial fibrillo-flutter (AFIFL) was registered, in these cases the atrial wave often had an undulating appearance Atrial dysrhythmia (ADY) was used as common designation for AFL AFI and AFIFL

QRS complex Low voltage was registered if no R or S wave in leads I, II or III was greater than 0 5 mV (Friedberg 1956) The amplitude of the precordial lead was not used as a criterion for low voltage (Watts and Gursel 1959)

The QRS complexes were examined for pathological Q waves and bundle branch block (BBB) according to the criteria of Blackburn et al (1960) Com

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plete BBB w   registered if the QRS-duration was $\geq$ 0 12 sec Left bundl branch block (LBBB) was registered if complete BBB was present and th ventricular activation time (VAT) in V_5 or V_6 was $\geq$ 0 06 ec. Right bundl branch block (RBBB) wa registered if complete BBB w s present and R was larger than R in V_1 Incomplete BBB wa not regist red as it cannot be dif fe entiated without difficulty from the electrocardiographic hypertrophy pattern.

Electrocardiographic igns of hypertrophy w re only evaluated in   ses with a QRS durati n of less than 0 12 ec Left ventricular hypertrophy (LVH) was evaluated according to the criteria of Hein et al. (1952) who only used the voltage signs of hypertrophy and th ventricular activation time (VAT) prol ngati n described by Sokolow and Lyon (1949) The crit ria were further mor modified according to th   riteria for normal values given by Simonsen (1961) The Heine criteria were ac   rdingly: $R_I+S_{III} > 2$ 5 mV o R in aVL > 1 1 mV o $RV_{5\ or\ 6}$ > 2 6 mV or VAT in $V_{5\ 6}$ > 0 05 sec or R in V_{5-6}+S in V_1 gre ter than the following valu s. men < 30 years $- \geq$ 4 4 mV men $\geq$ 30 years $-$ 3 6 mV women, irrespective of age $\geq$ 3 5 mV In addi tion, LVH was also evaluated using the Sokolow and Lyon (1949) criteri ex cept fo those relating to the T wave; th se were not used as high percen tag of patients had received digitali th apy The criteri for LVH accord ing t Sokolow and Lyon (1949) u ed in this study w e thu identical to those of H ine et al (1952) except that th voltage crit ria f r S in V_1+R in V_{5-6} were set at 3 5 mV as the upper normal val   irrespective of sex and ag   and S T dep   sions greate than 0 05 mV in l ad I or aVL o aVF or V_{5-6} were used as criteria if th T wave in th se lead was negative A   ri teria for right ventr cular hypertrophy either th   rit ria of Milno (1957) were used or those f Sokolow and Lyon (1947) the former being the m re strict: Fr ntal QRS axis > 110° r R/R^1 > S in V_1 and R/R^1 > 0 5 in mV in V_1 The   it ria of Sokolow and Lyon   ed in this study are as follows: R in V_1 > 0 7 mV o S in V_1 < 0 2 mV or S in $V_{5\ 6}$ $\geq$ 0 7 mV or R in V_1+S in V_{5-6} > 0 105 mV o R in $V_{5\ 6}$ < 0 5 mV or R $\leq$ S in $V_{5\ 6}$ or R in aVR $\geq$ 0 5 mV or R < S in V_1 o VAT in $V_{1\ or\ 2}$ 0 04 0 07 sec or R $\geq$ 0 5 mV and S T depr sion and negativ T wave all in V_1 r frontal QRS axi > 110° Combinations of th se crit r a f r LVH and RVH wer also egist ed.

LVH was also eval ated by alculating th sum of S V_1 and R $V_{5\ or\ 6}$ (in 0 1 mV) Furthermore th maximal QRS amplitud (i. th numerical sum of th R and S volt ge of th sam p ecordial lead) was calculated in V_{2-4} Similarly th maximal QRS amplitud of any prec rdial l ad was alculated.

The QRS axi in th fro tal plane was determined as follows. The method of Carte   Richt   and G een (1919) wa used with som modifi ations. In the r fig 8 th   ircle epre enting the diff rent axe was divided into 360 For the purpo   of simplific tion th circl in this examinati n w   divided int 24 areas: Area N 1 from 89 to 75   area N 2 from 74° to 60°   and are No 24 from 104° to 90° Th are   of th QRS omplex w re plotted on th ax   of fig 8 f Cart   et al. (1919) Th area of a QRS complex w s det rmined by onverting th QRS omplex to n o more tri angl s abov and below the isoelectric line: the area of the triangles were dded o subtracted   ccording to wh the they w   placed above o below th soelectric lin

The transitional one w s registered s the precordial l ad in whi h the R and S w ve ampl tud   w re most equal i size

The l tr al position f the heart w   det rmined according to Wilson (1944)

The ventr cular activation time (VAT) o intrinsicoid deflection w s de t rmined   the int rval betw en the onset f th QRS complex and the peak of th R wave If two p aks we   present (R and R^1) the one having the largest downstroke wa used (Friedberg 1956)

RESULTS AND COMMENTS

HEART RHYTHM

Table VI 1 show the distribution of patients according to rhythm. It is seen that roughly half of the cases had sinus rhythm (SR) Of the remaining patients again roughly half of them had atrial fibrillation. The frequency of the different rhythms within each MIS group did not show any obvious difference with the possible exception of group MIS 4 in which four out of five cases had sinus rhythm The one case of other rhythm of table VI 1 was case MI 46 In this patient no P waves were seen, but the R R interval was constant. Hafiz Khan et al (1973) reported a similar case (their case 1) in which the R R interval was constant but no P wave was seen in the surface ECG Atrial activity however was found by an intracardiac electrocardiogram. These authors felt that the absent P wave in the surface electrocardiogram was due to a low atrial voltage potential which they considered could be caused by extensive fibrosis of both atria. Table VI 1 also shows that premature beats (PB) occurred in four patients In these ca es the percentage of PB was small (< 10%) This repre ents a selection, a patients with frequent PBs were not found to be suitable candidates for the ha modynamic examination used in this study

The reported incidence of atrial fibrillation in mitral insufficiency vary much, probably reflecting the severity and duration of th disease and po sibly also the type of m tral regurgitation. Thu Jhav ri et al. (1960) reported that all their c ses of "relatively benign pure mitral regurgitation had sinus rhythm whereas Benti oglio t al. (1958) descr bed that 75 per cent of their patients with rheumatic mitral regurgitation of dynami significanc h d atrial fibrillation, Seltzer and Katayama (1972) found that 75 per cent of their surgical pati nts w th heumatic m tral regu gitation had atrial fibrillation wh reas this only occurred in 27 per cent of their surgical cas s of isolated rupture of chordae tendineae

Tabl VI 2 l sts xaminations for correlation between heart rhythm and other variable this examinati n wa carried out for all patient but also separately for p tients belonging to group MIS I. It is seen that the heart volum (CVI) the left t ial width (LAW) and th f nctional capa ity were signif cantly lower f r patients with trial dysrhythm (ADY) than fo patients with inus rhythm (SR) this w s most pronounced for the averag CVI which w s 63 per cent higher in ADY patients than in SR pati nts A diff renc in aver g cardi c index and average ag wa seen when pati nts with SR and ADY were c mpared these dif ferenc howev w e not tatistically significant. No differ nce w s found between ADY nd SR p tients r garding left atrial mean diastolic pr sure (LAMDP) and left atr al v w ve pressure (LAVP) When th examination was carried out fo p t ents in group MIS I (table VI 2) the ame trend was se n as for all the pati nt but no significant diff renc was found betw en patients with ADY and SR The st tistically significant correlation betw en heart rhythm and

Table VI 1 Heart rhythm

	Si bythm	Atri l fl tt	At i l fib il l ti	Atri l fib ill fl tt r	Oth r rhythms		Incid p m t f w <10 p r t	f b t ' m y ≥10 p t	11
MIS I	7	4	2	1	0	12	2	0	14
MIS II	2	2	3	0	1	7	1	0	8
MIS III	2	2	2	1	0	7	0	0	7
MIS IV	4	0	1	0	0	5	0	0	5
MIS V	5	0	4	0	0	8	1	0	9
MIS I V	20	8	12	2	1	39	4	0	43

Table VI 2 Correlation between heart rhythm and other variables.

Group	CI (1/ml /m²) A		LAMDP (mm Hg) Av		LAVP (mm Hg) A		CVI (ml/m²) Av		LAW (cm) Av		Funct group Av		Age A	
Rhythm	Range	(n)	Range	( )	Range	( )	Range	(n)	Range	( )	Range	(n)	Range	( )
MIS I V	2 58		12 4		25 6		595		10 8		2 4		38 1	
SR	3 9-1 7	(14)	22 1	(20)	69-6	(20)	970-360	(17)	13-9	(10)	5-1	(20)	51 17	(20)
MIS I V	2 12		12 4		25 1		968		14 6		3 2		44 2	
ADY	2 5 1 3	(16)	20-4	(22)	57-6	(21)	1680-470	(22)	19-11	(16)	4 2	(22)	60-34	(22)
p	> 0 05		0 84		0 98		0 00		0 00		0 00		0 08	
MIS I	2 34		11 6		34 0		688		12 0		2 3		39 1	
SR	2 5-1 7	(4)	19-9	(7)	69-10	(7)	970-360	(6)	13-11	(4)	3-1	(7)	48 23	(7)
MIS I	1 84		13 9		35 0		1082		15 0		3 3		42 1	
ADY	2 3-1 3	(5)	20-9	(7)	57 13	(7)	1680-470	(7)	18 11	(6)	4 2	(7)	51 34	(7)
p	0 29		0 38		0 71		0 07		0 26		0 07		0 71	

SR sinus rhythm ADY atrial dysrhythmia CI cardiac index LAMDP left atrial mean diastolic pressure LAVP left atrial v wave pressure CVI cardiac volume index determined roentgenologically LAW left atrial width funct group increasing number indicates increasing disability (chapter VIII)

CVI (and LAW) does not however indi ate wheth atrial dysrhythmia (ADY) causes enlargement of the heart (and the left atrium) or whether enlargement of the heart (and the left atrium) is the cau e directly or indirectly f the atrial dysrhythmia. It can likewise be discussed wheth decreased functional capacity is caused by atrial dysrhythmia, or whether th dysrhythmia indicates more severe heart disease which will also be a caus of the decreased functional cap city

P-Q INTERVAL AND P WAVE

Th P-Q interval is listed in table VI 3 According to the crit ria of Larsen and Skulason (1941) it is seen to be normal (< 0 22 se) in 17 out of 20 cas In the remaining 3 cases it was only slightly increased. Th prolongation of the P-Q interval was not confined to any specif c group

Bentivoglio et al (1958) found th P-Q interval increased in 3 out of 16 patients with SR suff ring from rheum tic mitral regurgitation f dynami ignificanc Olesen (1955) found increa ed P-Q interval in 4 out of 114 pati nts with isolated mitral stenosis and SR The incidence of prolonged P-Q interval thus appears to be small in ases of mitral valve disease as found in this and other studi s.

In only 2 cases w s the duration of the P wav longer than 0 13 sec which Larsen and Skulason (1941) regarded as the uppe normal value (table VI 3) In the sam tabl it is een that the P w v was bifid in 7 out of 20 case The first peak was th higher in one c se in 3 c s the second peak was the higher In the remaining 3 ses no obvious differenc was p sent. Th incidence of bifid or M shaped P waves appeared to be similar among the MIS groups. Bentivoglio et al. (1958) found a notched P w ve in leads I III in 10 out of 16 cases of mitral re gurgitation. Olesen (1955) found abnormally split P wav in 10 out of 114 case of mitral stenosis.

The durati n and amplitud of th terminal part of th P wave in p ecordial lead V_1 have been used for evalu tion f l ft atrial hyp rtrophy A seen from tabl VI 3 the total amplitude in V_1 w s small in thi mat rial. Th abov m n ti ned examinati ns could accordingly not be carried out on the available electro- ardi grams considerably high amplification of the voltage would have been necessary

Comparing th studi s of Bentivoglio et al (1958) and Olesen (1955) th inc denc of P-Q prolongation and abnormal P wav is possibly higher in cases of mitral regurgitation than in mitral stenosis; it is diff cult, however to com pare th severity of mitral disease in the two studi s mentioned. The small num b of cas within e ch MIS group with sinus rhythm does not permit any con- clusion to th relative incidence of the above mentioned abnormalities in this study

Tabl VI 3 P-Q interval and P waves.

G p	P Q (c)			P w d r tion (s c)		P wav M sh p d (in l ad I-III)		P wav amplitud in V_1 (mV)	
	<0 22	0 22 0 23	0 24	≦0 13	>0 13	yes	n	0 1	0 2
MIS I	5	1	1	4	2	2	5	6	1
MIS II	2	0	0	2	0	1	1	2	0
MIS III	2	0	0	2	0	1	1	1	1
MIS IV	3	0	1	4	0	2	2	4	0
MIS V	5	0	0	5	0	1	4	3	2
MIS I V	17	1	2	17	2	7	13	16	4
		20		19		20		20	

THE QRS COMPLEX

A pathological Q wave w s found in only one case (case MI 46) described in chapter IV This case will not be consid red in further examination of the QRS complex. The incidence of a pathological Q wave will naturally depend on the case m terial used for examination; in thi study c ses with mitral regurgitation secondary to myocardial infarction were not routinely examined by the present technique and were thu not outinely incorpo ated into this study

Low voltage was observed in the standard leads of one a e (case MI 1)

Bundle b anch block (BBB) was found in two cases (table VI-4) Ol sen (1955) found 5 case f BBB among 269 pati nts with pure mitral stenosis Bentivoglio et al. (1958) found 1 case of BBB among their 65 case of mitral regurgitation, Jhaveri et al. (1960) found BBB in 1 out of 47 cases of mitral regurgitati n. BBB thus occur arely in mitral valve dise

The average QRS axi in th frontal plane is seen from table VI 5 for all pa tients (except th patients with a pathologi al Q wav low voltag o BBB) The av age QRS-axis area numb r is similar in group MIS I t IV whe eas it is m re to the right in group MIS V but a considerable ov lapping occur Only 2 cases had a frontal axis of less than 30 both p tient had signifi ant mitral regurgit tion. Imperial t al. (1960) found a similar distribution among their p tients who were judged to have pure mitral stenosis p re mitral insuff ciency and combined m tral stenosis and insufficiency respectiv ly- this particularly apparent from their f g 1 which is very similar to tabl VI 5

As it wa app ent th t anothe factor than the mitral regu gitati n w effec ti in d termining the QRS frontal axis the ystolic pre sur in the pulmonary art ry w det rmined in 4 group of patient ccording to frontal axi area num ber- le than 10 10 11 12 and mo than 12 Th pulm nary artery pressure fo these 4 groups w s 41 3 35 7 42 0 and 58 4 mm Hg, spectively Thi differ nce between the 4 group wa statistically significant (p 0 04) Sto stein et al. (1962) similarly remarked that th presenc of right v ntricular hypertrophy (among their mitral valv di as pati nts) was m re relat d to pulmonary art ry p essure than to valve l sion

Th sum f S in V_1 and R n V_5 (or R in V_6) voltag i one of th m st impor tant el ment n th LVH crit r a f Solokow and Lyon (1949) (and of Heine et al. (1952)) In tabl VI 6 thi sum regist ed fo e ch MIS group The values are similar f ch group (with th po sibl exception of group MIS IV) The maximal amplitud (i. the num ri al sum of the R and S wav voltag in the same precordial lead) for precordial lead V_2 or V_3 or V_4 was calculated f r the patients within each MIS group N obviou difference w seen betw en the MIS groups (tabl VI 6) The maximal amplitude of any p ecordial lead was calculated f e ch patient within each MIS-group (table VI 6) Again n obvious differenc was noti ed between the MIS-groups. The transitional ne in the pre ordial l ad for ach MIS group i listed in tabl VI 7 N obvious diff rence

T bl VI 8 V lt p in precordi l l nd (in 0 1 mV)

G p	S V_1 + R V_5 6				M im l pli t d in V_2 V_3 r V_4			Maxim l ampli t d i a y V lead		
	35	35 ≦45	≧45	A	R nge	A	(n)	R g	A	(n)
MIS I	9	4	0	25 3	44 13	31 0	(13)	44 13	31 0	(13)
MIS II	6	0	1	25 6	44 12	20 6	(7)	44 14	24 6	(7)
MIS III	4	1	2	28 4	51 14	28 0	(7)	51 15	30 3	(7)
MIS IV	3	0	2	40 0	43 17	27 6	(3)	51 22	35 8	(5)
MIS V	7	0	2	30 3	62 8	30 8	(9)	64 12	30 9	(9)
All	29	5	7	27 3	62 8	26 8	(41)	64 12	30 4	(41)

T bl VI 7 Transit nal po ti n c rding to Wils nd VAT,

G oup	T ti 1 V_2	V_3	V_4	V_5	V_6	All	A	P siti n rding t Wils: V t	S ml rt	I t rm	VAT (0 01) V_1: R	S	A ( )	$V_{5\ 6}$: R	S	Av ( )
MIS I	0	3	5	3	1	12	4 2	5	5	0	3 1	1 9	(7)	6 2	3 9	(13)
MIS II	0	4	1	2	0	7	3 7	3	1	0	3 1	1 8	(6)	8 3	4 0	(7)
MIS III	1	3	0	2	0	6	3 5	2	2	0	10 1	4 0	(3)	5 3	3 7	(7)
MIS IV	2	2	0	1	0	5	3 8	2	2	0	2 1	1 2	(5)	6 2	4 2	(5)
MIS V	1	4	2	1	1	9	3 7	2	2	1	6-1	1 9	(8)	4-2	3 0	(9)
MIS I V	4	16	8	9	2	39	3 6	14	12	1	10 1	1 9	(29)	8 2	3 7	(41)

was present among these groups

The lectrical position of the heart was determined by the method described by Wilson (1944) The results among the 27 cases in which the ECGs could be placed in the groups set up by Wilson (1944) are listed in table VI 7 It is seen that *no obvious difference exists between the MIS groups*

The ventricular activation time (VAT) was calculated in V_1 and V_5 or V_6 The results are seen in table VI 7 No obvious difference is seen between the average values of the MIS groups Imperial et al (1960) likewise found no difference in VAT in V_1 comparing pure mitral stenosis and pure insufficiency (0 026 $^+$ 0 010 sec and 0 031 $^+$ 0 002 sec respectively) Bentivoglio et al (1958) found the VAT in V_1 to be an average of 0 03 sec in mitral insufficiency patients (with a range of 0 01 0 09 sec) The latter authors found that the VAT in $V_{5\ 6}$ was on the aver ge 0 05 sec (with a range of 0 02 0 09 sec) in the same group of pa tients Imperial et al (1960) found that VAT in V_6 was 0 056 $^+$ 0 004 sec in pa tients with pure mitral insufficiency compared to 0 038 $^+$ 0 008 in patients with pure mitral stenosis (the difference in VAT between the two groups was found to be statistically significant ($p < 0\ 001$)) The main difference between this study and the two oth r studies is thus that the average VAT in $V_{5\ 6}$ in the group of severe mitral regurgitation of this study was lower than in the other studies This difference may be expl ined by variations in the patient material with respect to duration of illness age the etiology of mitral regurgitation, etc

VENTRICULAR HYPERTROPHY

It is seen from table VI-4 that among the 39 patients who did not have an abnormal Q wave BBB o low voltage 21 p t ent had normal QRS complex 13 left ven tricular hypertrophy (LVH) and 4 right ventr cular hypertrophy (RVH) 1 patient having c mbined LVH nd RVH Among the 13 patients who had severe and domi nant mit al regu git tion, 5 had LVH and 2 RVH

It is diff cult to ompare the e findings to those in other studies as no study in which the mitral regurgit tion ha been measured is at present available In the studies discussed below the evaluation of whether mitral regurgit tion was present or not wa th mainly clinical or surgical in lecti n of p ti nts for study the p e enc of LVH establ shed by ECG may acc rdingly have been a contributory f ctor- thus McG ego and Zio (1955) stated th t electrocardio-graphic evidence of LVH n the ab enc of aortic valve di eas or hypertensi n has been ac epted by s s an ab olut contraindication f r surg ry The latter authors found LVH in 8 out of 13 p tients with ignificant mitral gurgitation (without stating th r riteri for LVH) Imperial et al (1960) ing the criteria of Sokolow and Lyon (1949) found LVH in 6 out f 15 pati nt with pure mitral regurgitation, Jhaveri et al (1960) ing the v ltag crite of Sokolow and Lyon (1949) found LVH in 9 out of 56 es with rel tively b nign pure mitral

regurgitati n Bentivoglio et al. (1958) found LVH in 19 out of 65 cases of mitral regurgitation of dynamic significance Am ng their cases of mitral regurgita tion, Ellis and Ramirez (1969) found an incidence of LVH of 48 per c nt in 42 p ti nts diagn sed clinically 35 per cent in 112 patients diagnosed at h art surgery and 77 per cent in 13 patients who had subvalvular mitral regurgitation; the cri teria for LVH in the l tter study were those of Sokolow and Lyon (1949)

From the above mentioned studi s and the pre ent study it an thus be conclu ded that a significant number of p tients with evere mitral regurgitation will not show evidence of LVH on ECG examination. This may be because eval ation of LVH by ECG gives a signif cant number of false negative sults; th presence of the latt r po sibility ha been proven among others by S ott (1960) and Allenst in and Mori (1960) An alternativ possibility is that th ventricular nlargement een in mitral regurgitation is cau ed by dil tation and hypertrophy ather than by hypertrophy al ne. It is thu notic able that in study of pati nts suffering from m re than slight aortic sten is (Hansen 1967) 45 out of 52 pati nts had evidence of LVH.

In th group with d minant mitral stenosis (MIS V) 2 out of 9 p tient were found t hav LVH (table VI-4) These two ca (MI 29 and 39) did not have art rial hypertension or other valvular dis ase at the time of the examination and belonged to the patients with optimal haemodynamic xaminati n (chapt IV) MacGregor and Zion (1965) found 1 cas of LVH among their 64 ca of severe mitral stenosis and ascribed this to moderate systemi hypertension but dded the above quoted remarks. Ellis and Ramirez (1969) found 3 per ent of LVH among 138 patients with pure and severe mitral sten sis. Th occurrence of LVH am g patient with dominant mitral st nosis could be tt ibuted ith r to pre ent or previous diseas affecting the l ft ventri l such a hypertension, ortic valve diseas and ischaemi myocardial di as o to fal positiv finding; in th diagnosi f LVH by ECG Sel er t al. (1958) and R nfeld et al (1961) found an inc denc of false positi LVH diagnosi of 17 and 13 per ent, r spectively

RVH was found in 2 out of 13 cas of dominant and severe mitral regurgitation (cas MI 11 and MI 18) but only the crit ri of Sokolow and Lyon (1947) were fulfilled. Th pulmonary artery systol pr ssure (PASP) was 107 and 33 mm Hg, respectively Using the crit ria of Sokolow and Lyon (1947) Jhav ri et al (1960) and Bentivogli et al (1958) found an incidence of RVH f 0/56 and 6/65 respec tively Using imilar riteria, Ellis and Ramirez (1969) found an incidence of RVH am ng the clinical th operated and the subvalvular case of mitral regurgi tation of 9 13 and 0 per cent respecti ly RVH thu does occur in sev re mitral egurgitati n, but not mmonly

C mbined vent icular hypertrophy was not found in any f th 13 cases in group MIS I with ev re mitral r gurgitation. Benti oglio t al. (1958) found 1 case am ng 65 ase of mitral regu gitation. In th 3 groups of Ellis and Ramirez (1969) mentioned abov combined v ntricular hyp rtrophy occurred in 12 1 and 8 pe nt, respectively The incidence of combined ventricular hypertrophy is

thus small in mitral regurgitation.

In conclusi n, atrial dysrhythmia occurred in half of all pati nts with severe mitral regurgitation. The presence of atrial dysrhythmia was correlated to in creased heart volume increased left atrial size and increased functional incapa city This correlation was statistically significant for th material in general but not for th group with severe mitral regurgitation, although the trend was present. In the patient with sinu rhythm approximately one third had M shaped P wave

Only two among 39 patients had a QRS axis in the frontal plane of less than 30^{o} both p tients had significant mitral regurgitation. The axis of the QRS complex was significantly correlated to the pulmonary artery systolic pr ssure

In the group with severe mitral regurgitation, 5 out of 14 patients had a left ventricular hypertrophy pattern. A left ventricular hypertrophy pattern, however also occurred among patients with insignificant mitral regurgitation. Based on this study as well as on the reports in the literature on patients with mitral valve disease it can be concluded that the absence of a left ventricular hypertrophy pattern does not exclude the presence of significant or even severe mitral regur gitation. The presence f left v ntricular hypertrophy suggests but does not prove that mitral regurgitation is present.

Chapter VII
Ultrasound examinations

Th purpose f thi chapt r is to evaluat ultrasound ardi graphy (UCG) in p ti nts with mitral insufficiency parti ularly as to whether the latiy degree f stenosi and regurgitation an be estimated from UCG in case of combined mitral dise se

MATERIAL

A th UCG apparatu w not btained until aft r a f w f the first haem dynami examinati ns had been arried out and t oc si nally was out f rde t w not po sibl t obtain a UCG xamination at the tim of haemo-dynami examination in all patients Thu in ord to obtain UCG examina tion in many pat ents po sibl som had t be xamined sub eq ent to their haemodynamic examinati n, but no p tients w re included in thi UCG study if an op rati n had been p rformed after th haemodynami examina ti n.

Accordingly thi hapte includ 36 cas am ng th 43 cas d scribed in chapt III.

Tabl VII 1 describe th tim int rval between th ha modynamic examin tion and th ultrasound examination. Thi interval vari b tw en 0–61 months with an verag f 25 m nth It en from th tabl that th av rag valu f th interval long f the patient with significant mitral re gurgitati (MIS I + II) than fo th se w th a significant mitral st no (MIS III + V) Howev r onsid rabl ov lapping al an among the MIS groups. Although t is likely that som chang will hav occurred during th int rval t felt unlikely to hav affected th correl tions between the vari able d scribed in thi chapt e g if maximal diastolic veloc ty w s signi f antly ed ed t th time of ha modynami examination, t seem unlikely that t would hav incre ed some m nth lat t th tim of th UCG exami nati n. Thi howev has not been prov n.

METHODS

Th techniqu and theory of UCG examinati n have been d scribed in detail in th monograph by Edler (1961) and Gustav on (1966) s well as in sh rt articl by Segal t al. (1966) and Zaky et al. (1967) to which reference s m d f detail

T bl VII 1 Time int rval b tw n heart c th t izati n nd UCC examination

Gr p	<6 mo th	6 23 m th	24 47 month	>47 month	All	Range	Av
MIS I	3	1	3	4	11	54 0	30 8
MIS II	2	0	3	2	7	57 0	35 0
MIS III	3	0	1	1	5	61 0	17 2
MIS IV	1	0	4	0	5	47 0	31 2
MIS V	5	0	3	0	8	39 0	13 7
All	14	1	14	7	36	61 - 0	25 2

In this study an Ekoline 20"[1] was used in obtaining the UCG A bell shaped transducer was applied to the chest. The transdu r produced ultra sound waves of 2 25 meg cycles with a pulse rate of 200 pul es per second. Th echoes were received by the transducer and displ yed on an oscilloscopic screen in the "A form indicating their distance from th anterior chest wall and their relative strength. By means f a slow sweep unit th trace could be moved across the oscilloscope Thi tracing could then be photographed. Lit points were seen on the photograph indi ating 1 cm of distance as well as timing (every second) A photograph thu ontained tracing which could be used for calculations Alt rnativ ly the motion of the mitral valve was transferred to a direct writing Elema ink jet reco der[2] A plexi glass block with steps for 6 7 and 8 cm distance was used for calibration on the Elem recorder The letter numbering of Edle (1961) will b used for describing the UCG tracing (fig VII 1 (A))

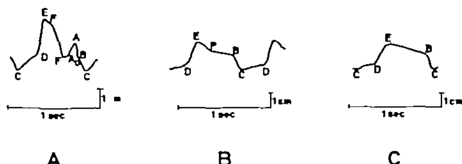


Fig. VII 1 Ultrasound ardiogram showing th movem nt of the anterio mitral leaflet. E is the most anterio point and C th most post ri r point. Th tr cing from B to D indic t th movement in systole. D to F shows valve opening E t B ind cate th movement in th remaining part of the di stole the A wav c rrespond to th atrial systol D wing A i normal cusp movement. D awing B and C indicat signif cant mitral st no- s es by th pl teau form tion starting at point P and E (in drawings B and C spectively) and nding at point B For furth explanation see p 139 140

Each p tient w examined in the supine position, th chest being elevated to comfort ble position with an elevati n f 30°-45 f th bedhead The echo f the anterio mitral valv w s ecognized as a fast moving ech and was recorded at three diff rent po ti ns in th prec rdium if possible The maximal veloc ty of mov ment in arly diastol (MDV) as w ll a oth vari abl we e alculated in s many diastol possibl Th pape speed of th Elem record w alway 5 cm per second.

Since the nitial studi s of Edl (1955) the maximal diastoli velocity of th ant ri mitral valv (MDV) ha been shown to give val abl informati n in se of mitral stenosi (Eff rt 1959 Gustavson 1966) Gustavson (1966) u ed th t rminology diastolic d ec nt rate" and Segal (1966) similarly used slope of the E w e As the tra ing from whi h MDV is calculated a distanc v su time recording th terminology MDV w bosen. In thi stud MDV wa calculated using th steep st line which would fit the curve from E to B e g Fo-F

Tabl VII 2 list th sults f measuring MDV in 10 pati nt in whom th m surement were p rf rmed at 3 different positions n the chest wall. The

1) "Ekoline 20 Mark One from Smith and Kline Instrument, Inc. 440 Page Mill Road Pal Alto California 94306 U S A.
2) Elem Mingogr ph 31 or 34 from Elema Schönande Solna Sweden.

Tabl VII 2 Compari on betwe n m ximal diastolic velocity (MDV) measured at different positions on the chest

A	MDV in 3 diff nt h t p iti (/)			T t l g f MDV (/)		no f m(ti ms withi h p iti			SD of all MDV m a r me ts (/s c)	p	SD of MDV me urem nt within n positi n
4 1	42 4	40 8		58	36	17	14	7	3 6	>0 05	4 2
13	14 6	14 8		18	10	10	14	7	3 0	>0 05	2 2
6 4	47 4	64 2		82	40	17	14	14	30 4	<0 01	9 4
13 4	19 8	18 6		22	10	17	8	6	9 2	<0 01	2 4
29 4	18 2	14 6		34	8	6	7	4	19 8	<0 01	4 8
11 2	11 2	16 8		26	10	11	4	7	6 8	>0 05	4 0
25 0	29 4	25 0		34	20	11	6	4	6 4	>0 05	3 6
27 4	22 8	22 6		38	18	17 -	14	11	10 6	<0 05	5 0
38 2	42 2	41 4		54	32	7	4	11	5 2	>0 05	5 2
34 2	32 6	36 2		42	24	9	4	7	4 4	>0 05	5 2

Th p value indi tes th significance of difference between the MDV measurements in the three different positions

average values differed significantly between the 3 pos tions in only 4 of these p tients These finding are similar to those of Gustavson (1966) An appre ciable variation also occurred between the MDV values within each position.

MDV in this study was determined using the Ekoline "Elema recorder system or the Ekoline photographic system The former has the advantage of providing a number of heart cycles during whi h the MDV can be calcul ted, but it is time-c nsuming particularly if the echo of the anterior mitral valve is w ak. The latter method give only few determinations but is les time consuming

MDV determinations obtained nearly simultaneously u ing the two methods were compared in 18 patients; the MDV of the Ekolin Elema system was th overall average of all the values obtained. The Spearman correlation coefficient (R) was 0 87 and th p-value 0 0000

As a consequence f the above menti ned examinations the MDV valu listed in this study (unles otherwise menti ned) will b th total average of all MDV dete minations obtained using the Ekoline" Elema system or if this is not availabl the MDV value obtained using the Ekoline photographic system.

Gässl r and Samlert (1958) and also Kl in (1969) h ve d scribed a corre lation betw n MDV and heart rat In order t examine thi the MDV was determined in 35 patient as wa th R R interval of the preceding heart beat; patients we only included into this examination if a minimum of 5 MDV me surem nts had been obtained (th numb of MDV determinations thus varied from 5 t 36 th ave ag being 20 4) Th R R tim interval then wa examined fo correlation to MDV Such correlation was found in only 4 of the 35 pati nts; sinus rhythm was pr sent in all of th se 4 pati nts No definite correl tion between h art at and MDV has thus been found in gene al, thi result i in disagreement with the finding of the p eviously men tioned authors but similar to thos of Gustavson (1966) A cordingly no attenti n ha been paid to the h art rat in the calcul tion of MDV

Measurement of th total amplitud of th ant ri r mitral cusp movement (TA) ha be n found valuable in th study f mitral stenosis, as TA wa re duced in the patients with th fixed and immobil mitral leaflets (Segal et al. 1966) In this study th ampl tud wa alcul ted by placing a rul r on the E p ak of a UCG tracing and l t on th C points The distance betwe n the two lines was me sured, th value w expre sed in m aft r correcti n for amplif cati n. According to Gustavson (1966) TA shows only small varia ti ns in th sam p ti nt.

Th d astolic amplitud of the ant rior mitral cusp m vement (DA) was measured as th verti al distanc b tw en po nt E and point B using a rul r (as d scribed fo TA measurem nt) and corrected fo amplification. Thi determination wa only arried out if point B and E w re well-defined points.

The configuration of the UCG tracing has been used for drawing concl sions as to th p e nc o b nc of mitral regu gitati n.

Schmitt and B aun (1970) conside ed that if th UCG tracing from point C through point D t E w s onc v and without sharp angulation at point D mi tral st nosi was dominant. On the other hand if the tracing from C to D w relatively sharply rising with an almost vertical line from D to E giving a sharp angulation at point D then mitral r gurgitation w dominant. The UCG tracing of thi study w re the fo e examined t se wheth they wer rounded r had a sharp angulation t point D Case wher this ould not cl arly be decided did not nter into this valu tion.

Edle (1968) well Friedman (1970) have reported th t point E w ounded in patient with significant mitral st no i whereas a sharp angl w s seen in patient with m tral egurgitation. It was accordingly noted whe ther the UCG tracing at point E was ounded or had a sharp angle

The shape of the UCG tracing in diastole (from point E to point B) ha been desc ibed by S gal et al. (1967a) a providing information on the pre

sence of mitral regurgitation: A rapid initial slope followed by a plateau indicated dominant mitral regurgitation and mild mitral stenosis. Paller et al. (1970) have made similar observations. The latter authors paid special attention to the meeting point of the rapid slope and the plate u (this point will be referred to in the following as point P) (fig VII 1 (B)) According to these authors decreasing vertical distance between point E and point P indicated decreasing important mitral regurgitation in combined mitral disease similarly an increasing vertical distance between point E and point P indicated a decreasing factor of mitral stenosis They also stated that a small ratio between the vertical distances E P and D E likewise indicated that mitral stenosis was an increasingly important factor

In this investigation, the diastolic part of the UCO tracing was studied as follows It was noted whether any plateau formation took place or not and the ratio was calculated between the vertical distances E P and D E In a typical case of tight mitral stenosis without any mitral regurgitation, a straight line from point E to point B would be seen to deviate only slightly from a horizomal line (fig VII 1 (C)) points E and P would be combined and the E P/D E ratio accordingly 0 0 If no mitral stenosis was present point P would be identical with point F and at the same level as point D (fig VII 1 (A)); a typical stenotic plateau would accordingly be absent and the ratio E P/E D could be regarded as being 1 0

RESULTS AND COMMENTS

MAXIMAL DIASTOLIC VELOCITY (MDV)

Table VII 3 lists the average MDV values of each MIS group. The value is seen to be decreasing from group MIS I to MIS III but a considerable overlapping exists. It is also seen that it apparently does not make any difference which method in general is used for calculation of MDV (of those listed) The most surprising finding is perhap the very varying and particularly the low MDV values of group MIS I 338 330 164 118 60 40 34 32 8 20 14 mm/sec Fig VII 2 shows that no correlation exists between MDV and the r gurgitant fraction (RFLVO) A Spearman analysis of the correlation between the two variabl s (n 38) gave a corr l tion coefficient of only 0 29 and a p value of 0 08 If however only those ases which had a mitral val e gradient of l ss than 5 mm Hg were included in the analysis R was found to be 0 68 and p 0 01 Th two patient wh had a high MDV (> 300 mm/sec) also h d a severe mitral egurgitati n (RFLVO being 0 86 and 0 67 respecti ely)

From table VII-4 it is seen that DV correlate signif cantly with mitral alve gradient and mitral alve area 4 patients who had no roentgenologically proven calcification f th mitral val had an a e age MDV of 47 5 mm/sec compared to 60 3 mm/sec in 10 pati nt wh had m tral valve calcification, thes aver ge values were not statist ally d ff rent (p 0 47)

The following normal DV al s (in mm/ ec) h ve been reported as rang (and average) Eff rt (1959) 200 86 (12) Joyner and R ed (1965): 170 83 ( ) Segal et al. (1966) 1 0 0 ( ) Edler (1967) 190 90 (140) Among the eleven patients belonging to group MIS I (and acc rdingly with severe and dominant mitral

Tabl VII 3 Maximal d st l o velocity (MDV) in mm/ ec ac rding to MIS groups nd techniqu of ec rding

	Ek ll "-"Eleme ystem Ek line photo-graphi sy tem			"Ek line" Ma imal i dividual lue			"Elem sy t m" Minimal i di idual value			Average i dividual value			"Ekolin phot graphi y tem"		
G oup	Range	A	( )	Range	A	( )	Range	A	( )	Range	A	( )	Range	Av	(n)
MIS I	338 14	107 2	(11)	350 22	104 0	(10)	326 8	72 6	(10)	338 14	85 0	(10)	330 10	96 0	(9)
MIS II	84 22	50 4	(7)	94 28	51 6	(5)	68 16	36 2	(5)	84 22	44 2	(5)	86 18	49 0	(5)
MIS III	52 14	32 2	(5)	82 18	22 8	(5)	40 10	12 2	(5)	52 14	32 2	(5)	24 14	20 0	(3)
MIS IV	122 26	59 6	(5)	136 30	84 2	(4)	72 20	43 6	(4)	122 26	63 0	(4)	84 18	57 4	(4)
MIS V	44 12	24 8	(8)	68 12	32 2	(7)	24 8	15 4	(7)	44 12	23 0	(7)	38 20	27 8	(3)

Maximal individual value indicates that the maximal MDV value h s been calculated for each patient. Similarly minimal individual value and average individual value indicate examination of the minimal and average MDV value respectively for each patient.

Table VII-4 Correl tion between maximal diastolic v locity (MDV) and mitral gradient (CRAD) or mitral valv ar (MVA).

C d (Hg)		MDV ( ) /		MVA m^2	n	MDV (v) m/ c
<5	12	97 0		>2 4	12	69 2
>4 <10	16	52 0		<2 5	11	35 0
>9	8	24 2				

p < 0 02 p < 0 05

regurgitation) the majority (seven) thus had an MDV below the lowest quoted normal value (70 mm/sec) and only 2 had an MDV above the highest quoted normal value (200 mm/ ec)

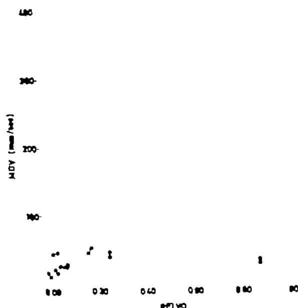


Fig. VII 2 Maximal di stoli velocity (MDV) of anterior mitral leaflet move m nt in relation t egu gitant fraction (RFLVO)

Segal et al. (1967a) stated that an MDV of less than 50 mm/sec. se n in ases of combined mitral stenosi and insufficiency and c ted d minant mitral stenosis and mild mitral reflux' In the pre ent study 6 out of 11 patients who had sever mitral gurgitati n and UCG performed had an MDV below 50 mm/sec th study thus in disagre ment with that of Segal et al. (1967a) who determined the dominant lesi n primarily by the degree of mitral reflux demonstrated by cine adiography of th l ft v ntricl Eff rt (1959) st ted that below 20 mm/ e no haemodynamically signif ant regurgitation occurs However n the group of sev e mitral regurgitation in this study two patients had low MDV val es of 20 and 14 mm/sec respecti ely S milarly among the 7 patients who had mod ate regurgitation and no significant m tral stenosis 3 out f 7 had MDV valu below 20 mm/sec (Eff rt (1959) did not describe his method for evaluation f mitral regurgitation) Werning (1970) expressed hi opinion more carefully an MDV of l than 20 mm/ ec place mitral stenosis in the front are but did not specify the ason for hi opinion. Wharton (1969) also stated that if MDV was l s than 40 mm/ ec stenosis was dominant ; n information as t the eval ati n of mitral egurgitation was given. C ntrary to these authors Winter et al. (1969) d scribed findings similar t those of the present study in 4 patient w th clinically pure m tral insufficiency who had cineangiocardiography

and in some cases evalu tion of mitral regurgitation performed at operation. 13 out of these 24 patients had normal or increased MDV but in the remaining 11 patients MDV was les than normal. 56-40 mm/sec in 3 cases 39 20 mm/sec in 5 cases and less than 20 mm/ ec in 3 cases

In agreement with the latter author the conclusion must be that a reduced or even a severely reduced MDV does not rule out significant or severe mitral re gurgitation, but only indicates that the anterior mitral leaflet moves abnormally- the ca se of this abnormality is probably fibrosis and shrinking of leaflets and chordae but this ha not been examined in the present study- it should however be noticed th t the presence or absence of mitral valve calcification did not cor relate with MDV

In two case MDV was higher than normal 338 and 330 mm/sec respectively Segal et al (1967b) hav described abnormally high MDV of 150 250 mm/sec in mitral regurgit tion. It is tempting t ascribe this abnormality to mitral regurgi tation without major stru tural deformity of the anterior leaflet. Sweatman et al (1972) however described normal MDV in 4 out of 6 patients with rupture of the chordae tendineae to the posterior l aflet. This does not however rule out that increased MDV could be seen in rupture of the chordae tend neae to the anterior leaflet but the pre ent study does not allow for any conclusions in thi respect.

AMPLITUDES OF ANTERIOR ITRAL CUSP MOVEMENT

The t tal amplitud f anteri mitral cusp movement (TA) is listed in table VII 5 accordi g to MIS groups. It is seen that the average TA decline from group MIS I to IIS III but is simil r in group MIS III and V Con ider ble over lapping is seen betwe n the IIS group indicating lack of correlation between degre of regurgit tion and TA.

In a s tt rgram between TA and the degree of mitral regurgitation (RFLVO) no c rrelati n was see b tween th se two variabl s (fig VII 3) A Spearm n ex minati n of corr l tion g e a correlati c fficient of 0 02 and a p val e of 0 89 (n 36) I c with a di stolic mitral val e gradient (GRAD) of l ss than 5 mm IIg h we e the c rrelati n coefficient (R) w 0 61 and the p val e 0 03 (n 12)

The ormal al f TA which h been eported are rath r simil r to judg from th stated rang f al es (in cm) Segal t al (1967) 3 0 2 2 Edl r (1967) 3 3 2 0 Winter t al (1967) 4 0 5 Wharton (1969) 2 7 1 9 If 1 9 cm l used as the low normal TA value 3 out f 11 p tient with dominant nd evere mitral regurgit t (group MIS I) and 3 out of 8 patient with significant r gurgit ti n without gnif cant st no is (group IIS II) had a signifi antly red ced TA (table VII 5) Thi di gr ment with Segal t al (1967a) s well as Wh rton (1969) s th l tt r did not find ny ca e f decr sed TA among hi 17 patients with mitral gurgitation. Winth r et al (1969) in their previou ly

Tabl VII 5 T tal ampl tud f nt l mitral l flet movem t (TA) i m

G p	A	s	M	s	N mb f p ti t with TA <1 9	1 9 2 7	2 8 3 7	>3 7
MIS I	2 53		3 8	1 2	3	4	3	1
MIS II	2 17		3 4	1 3	3	2	2	0
MIS III	1 97		2 6	1 6	3	2	0	0
MIS IV	2 48		3 5	1 8	1	3	1	0
MIS V	2 01		2 6	1 3	4	4	0	0

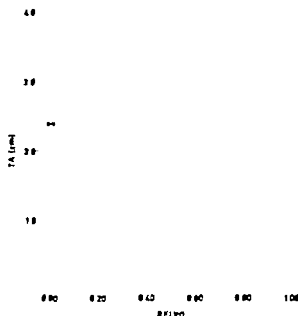


Fig VII 3 Total amplitude (TA) of anterior mitral leaflet movement in relation to regurgitant fraction (RFLVO)

mentioned study of 4 p tients with pure mitral insufficiency found a similar di tribution of case ccording to the groups in table VII 5 as in the pre ent study < 1 0 cm. 6 1 9 2 7 cm: 10 2 8 3 7 cm 7 > 3 7 cm: 0 It must be concluded accordingly that som p ti nts with ignificant mitral regurgitation (without significant mitral stenosis) have reduced TA (Using the surgical evaluation at operation as an e timate of th mitral regurgitation, Gustavson (1966) found in combined mitral disease a statistically significant reduction in TA with increasing regurgitation, an average of 2 09 cm for c ses without significant regurgitation rsus 1 75 cm for c ses with significant regurgit tion)

Table VII 6 C rrel tion between mitral valve gradient (GRAD) and th total amplit d f t ri mit al l aflet (TA)

G d (Hg)	TA (m)	
< 5	2 79	12
5 9	2 03	16
> 9	1 93	8

p 0 017

In the present study table VII 6 shows a statistically significant co relation between mitral valve gradient and TA. TA, however was not correlated to mitral valve area (MVA) as patients with a MVA of less than 2 5 cm^2 had an average TA of 2 04 cm (n 11) ompared to an av rage TA of 2 27 m f th se patients (n 12) with an MVA larger than 2 5 cm^2 these average val wer not significantly different ($p > 0$ 05)

As described in chapter V the presenc f cal ifi tion in the m tral valve wa evaluated by tomography of the heart Among th 10 p ti nts with proven cal cifi ation, th average TA was 1 93 cm compared to 2 29 cm in the 24 patient in whom no calcificati n could be demonstrated; thi differ nc was not statisti al ly significant. G stavson (1966) proved that a correlation w pres nt betw en the degree f alcificati n (s registered by the surgeon t operation) and TA. Winthers et al. (1969) among patients with pu mitral insufficiency found that 5 out of 6 pati nt with mitral valve calcific tion had TA of 1 6 m o 1 ss; in 5 patient with no calcific tion, normal or slightly redu ed" TA w described, this study did not specify the m thod for eval tion of mitral val e alcifi ation. It has thu not been definitely prov n th t calcif cati n i c rrel ted to TA as an evaluati n f al ifi ti n during surg ry might include other factors than true calcification.

In this study one p ti nt (se MI 31) wa found to have an increased TA of 3 8 m (thi patient also h d inc e sed MDV) Segal t al. (1967b) rep rted as described earlier that TA w g nerally ncre ed in mitral regurgitati n and quoted an amplitude f 4 2 m the high st al S gal t al (1967b) mment ed that p ti nt with flail mitral l aflet usually d monstrat a larg amplitud

In conclusi n, p ti nt with ignifi ant m tral egurgitation may demonstrat low normal o high TA val A low TA thu doe not indi ate that mitral st n sis s th dominant l si n, but th t signif ant valvular or ch rdal d form ty present. A high TA possibly indi t signif ant mitral regurgitation with only littl def rmed ant ri r mitral usp a een i a flail l aflet due to chordal rup ture or papillary muscl dysfunctio but thi has not been inv stig ted in th present study

Th d stoli mplitud of th ant ri m tral cusp movem nt (DA) i the v rtical dist nce b tween point E and point B in th UCG tracing In table VII 7 thi val li ted for ach MIS-group Th e i no pparent m jor diff enc in v g valu betw en th MIS groups (except f group MIS IV) and considerabl overlapping p sent. A sc tt gram between th d gr e f mitral regurgitation (RFLVO) and DA did not show any correlation between the variabl s. Evaluated by the Spearm t st, no correl ti n w s pr nt between th two variabl s, s th orrelation coeffic nt wa 0 20 and th p valu 0 33 (27) Few patients (6) with small mitral g adient wer available for this correl tion examination; th R val w 0 00 and th p-val >> 0 05 As seen from table VII 6 DA was signifi antly c rrel ted to gradient nd to valv area. Th determination of DA acc rdingly did not help in evaluation f the degr e of mitral regurgitation.

but correlated well with the degree of mitral stenosis

Table VII 7 Distribution of amplitude of diastolic movement (DA) according to MIS groups

Gro p	Av (m)	Ra g (cm)	n
MIS I	0 90	1 57 - 0 39	8
MIS II	0 86	1 02 - 0 63	3
MIS III	0 74	1 02 0 48	5
MIS IV	1 34	1 95 1 01	5
MIS V	0 61	0 93 0 48	8

CONFIGURATION OF THE UCG TRACING

Table VII 9 lists the results of an examination of the C D E tracing for th pr sence or absence f a harp angle at p nt D As een from the t ble a sharp angle was found t point D in all except 3 cases and these 3 cases were found in 3 different MIS groups This tud therefore does not support the contention of Schmitt and Braun (1970) th t the configuration of the C D E tracing would indicate whether mitral st no is or mitral regurgitation was d minant (as described in Methods) but the d termination of whether a curve has a sharp angl or not is naturally a matt of subjective evaluation.

The shape of the UCG tracing at point E is also se n from table VII 9 As seen from this tabl th re wa no obviou differenc betwe n group MIS I and MIS V as to th percentage of patients with a rounded E point. A seen fr m table VII 10 the pre ence of a rounded E point w s not correl ted to the degree of regurgitation (RFLVO) however a correlation w s found to the mitral valve gradient. No particul rly high incidence of mitral val e calcification was noticed amo g pati nts with rounded E point (5 out of 14 p tient) s calcification was also found in 4 out f 16 pati nts who did not have a rounded E point Thi stud thus confirms the impr ssi n f Edler (1968) and Friedman (1970) a to th val of evalu tion f the E point f mitral stenosi but not f r mitr l r gurgit tion.

T ble VII 8 C r elation between amplitud of diast lic movem nt (DA) versu mitral valv gradient (GRAD) and m tral alv ar (MVA)

G di t (mm Hg)	n	DA ( )
< 5	6	1 25
5 9	13	0 87
> 9	8	0 65

p 0 002

Mit l l m[2]	n	DA m ( )
> 2 4	9	0 95
< 2 5	11	0 69

p 0 01

Tabl VII 9 C nfigur ti n f I CG t cing

	C D F		E p i t		St ti pl t			E P/E D atio	
					A	B	C		
		Sh p		Sh p	At	L t r	N		
G p	R d d	gl	R d d	gl	E p i t	th E	Pl t	A	I group B
MIS I	0	8	5	4	2	2	7	0 7	0 3 0 7
MIS II	1	4	1	4	0	3	4	0 8	0 3 0 5 0 6
MIS III	1	3	4	1	2	3	0	0 2	0 2 0 3 0 5
MIS IV	0	4	1	3	3	1	1	0 3	0 4
MIS V	1	6	3	4	6	1	1	0 2	0 2
	3	25	14	16	13	10	13	0 4	

Table VII 10 Correlation betwe n the shape of E point ve sus the degre of mitral egurgitation (RFLVO) and mitral valv gradient (GRAD)

E P i t	RFLVO		GRAD (mm Hg)	
R und d	0 297		9 0	16
Sh rp gl	0 310		5 7	14
P	> 0 05		0 02	

The shape f th diastoli part f the UCG tr ing was evaluated a described in Methods and the results listed in table VII 9 It i se n that in the group of severe mitral regurgitation (MIS I) 7 out f the 11 p ti nts did not hav any stenotic plateau, whereas in the group f signifi ant mitral stenosis without ignificant mitral regurgitati n (MIS V) this plat u was only absent in on c s Similarly only 2 in group MIS I had mbined E and P point compared to 6 out of 8 in group MIS V However ov l pping occurred among all MIS groups From tabl VII 11 st tisti ally significant correlation is seen betwe n t) shape of the diastoli part f the UCG tr cing and th degree f regurgitati n the average regurgitation (RFLVO) being high st wh n no stenoti plat au is present and maller wh n th stenotic plateau begin t the E point Th mitral valv are w s similarly high st when no st noti plat au w s pr sent ... verse relation to diastolic gradient w s pr se t th gradi nt being l igl ... the plat u started at th E points. Th MDV was similarly ignificantly ... l ted to th shape of the tracing, being small st when th pl te u starte ... E point.

If th p ti nt w e grouped according t the siz of th mitral (GRAD) (< 5 5 9 and > 9 mm Hg specti ely) th av rage l l /l, 0 71 0 50 and 0 05 respectiv ly (12 16 and 8 espectively); in verag valu w statisti ally signifi ant (p 0 003) If the ... grouped acc rding to the degr of mitral regurgitatio (RFLVO ... 0 10 < 0 10 respecti ly) the ag EP/ED rati was 0 70 respectively (11 12 and 13 respectively) the differenc ... statisti ally signif ant (p 0 03) No rrelation w found ... the pre nc ab nc of mitral valv alcif ation and EP/I ... ati w 0 39 in th f rmer ase and 0 46 in th latter; this ... statisti ally signif nt (p 0 58)

Thi study ha thu gen all confirmed the observ ... and Pail et al (1970) Acc rdingly abs nc of a sten... tracing case of mitral valve dise e sugg sts that m ...

Tahl VII II Co r lati n b tw n th h p f th diastolic curve and oth r vari bl

Pl t f m ti	R g rgitati (RFLYO)	Gradi nt (m Hg)	V lve re (cm^2)	MDV mm/ ec
At E p nt	0 170	9 5	2 1	22 0
L t r th E	0 316	6 4	4 0	43 4
N pl t	0 434	3 5	7 5	114 8
	14-9 13	14 9 13	13 7 3	14 9 13
p	0 014	0 001	<0 05	0 00

significant. Similarly plateau formation t the E point or cl se to it suggests that mitral stenosi is significant. This is a general rul however and exceptions to the rule do unfortunately exist a seen from tabl VII 9

IN CONCLUSION

In thi study examination of mitral pati nts by ultrasound cardiography was only found to be moderately helpful in evalu ting whether signifi ant mitral regurgita tion was present or not. The best help wa obtained by inspecti n of the diastolic tracing, as 11 out of 13 p tients wh did not have a stenoti plate u had signi ficant mitral regurgitation, and as 9 out of 13 p tients who had a "st notic pla teau at th E point did not have significant mitral regurgitation. Ov lapping prevented these principl s from being reliable riteria. Th maximal diastolic velocity proved to be more disappointing, with the possibl ex eption that signi ficantly high MDV indic tes significant regurgitation; in particular a low MDV does not rul out significant mitral regurgitation. None of th othe UCG variab l examined proved to be of any help in predicting th degree of mitral regu gi tation.

In contrast to regurgitation, almost all UCG variabl e amined in this study orrelated well to mitral valve gr dient and most, but not all, to mitral valve area.

ADDENDUM

In th xaminations d scribed abov only the anterior mitral leafl t has been m ntioned. Rec nt techni al advanc howev hav permitted examinati n f the posteri m tral usp in addition. Normally both leaf lets come togeth r in arly systole nd stay together throughout systole during which tim th re i a gr dual anteri moti n of both leaflet (Dillon t al 1971) Millward et al (1973) ompared th UCG findings in thr groups f p ti nts: In heumatic valvular mitral regurgitation no separation was found betw n th ant ri and post ior mitral cusp in systol In patients with ruptu of the bord e t ndin and in patients with congestive ardi myo- p thy and typ al api al bol systolic murmur" systoli separation of the m tral leaflet w found The l tt r group of pati nts had a reduced ampli tude f ant rio mitral val e movem nt (as m asured from point D to point E) a ompared to th p tients with ruptur f th chord (p 0 05), but onsid rable overl pping occurred between thes two groups. In three pa tients with ruptur of the chordae tendineae to th post rior cusp Sw tman et al. (1972) reported a posterior movement of that leaflet in systole Kerber et al (1971) d scribed an abrupt posterior movement of eith th anterior th posteri r mitral cusp in l t systol in 9 out of 10 patients with systo lic cli k and l te systoli murmur

Popp and Harrison (1970) stimated LV stroke volum by det rmining LV dimension in systol and diastol When this stroke volume det rmination w mpared with determinati n of stroke volum using the Fick principle the everity of mitral regurgitation could b d termined; thi det rmination of mitral regurgitation w reported to compare well with stimates using angiocardiography

Chapter VIII

Clinical observations

Thi chapter i c ncerned with the anamn tic information, symptoms and clinical finding Th aim has not be n to d scribe ev ry aspect of clinical ob ervati ns in p tie ts with mitral r gurgitation, but to report and comment on those ob rva tions actually made in this st dy particularly if they could be regarded as useful in eval ti g the rel tive degree of mitral regurgitation (and t nosi) It has like wi e not been the purpose to discu s the pathog nic mech nism of ymptoms and igns

For inf rmatio on th general auscultatory and clinical finding n mitral di ea the reader is referred to the review of Brigd n and Leatham (1953) Wood (1954) P rloff nd Harvey (1962) Nixon (1964) Py et al (1966) and Hultgren t al (1968)

IATI RIAL

Th s tud incl de the 43 p t ent d scribed in chapter IV ("Materi l) Th p ti nt w r divided into 5 group (MIS group) o al o described in ch pt r IV (" t r al)

Th dist ibuti of th mat rial accordi g to g i e n from tabl VIII 1 Th ag i s mil f ch IIS group except f r group MIS IV in whi h both th av rag ge nd th high t nd lowest age with n th group were l w r th n in an of th oth MIS group

The di ribut rd g t i also e fr m t ble VIII 1 In this st d the aver ge f al t mal ti w 1 to 1 Ole n (1953) found f male t mal rati f 5 t 1 F min t of p t nt w th m tral n si B ti v gllo et al (19 1) found femal to mal r ti f 0 t 1 m g their p ti nt with adv nced heum t c mitral r gurg t ti n S lzer nd F t am (19) found a f mal t r al r ti f 1 to 1 in th i group f p tient l ving rheum tic

Table VIII 1 Age and ex according to MIS group

C o p	Ag (y r) Av	(R g)	S M l	F m l	T t l
MIS I	40 6	(51 - 23)	8	6	14
MIS II	42 3	(58 - 23)	1	7	8
MIS III	43 7	(52 34)	4	3	7
MIS IV	34 4	(44 17)	1	4	5
MIS V	45 2	(60 34)	3	6	9
MIS I V	41 5	(60 17)	17	26	43

mitral gurgitati n. Jhaveri et al. (1960) found femal to mal r tio f 4 6 to 1 among their p tient with elati ely benign pure mitral regurgit ti n of rheu m ti origin th se autho omm nted that the bed w e not always equally vailable fo both sexe In patients with solated rupture of chord e tendinea Seltz and K t yama (1972) f und m h low f male t male r ti (0 2 to 1) C ves t al. (1973) also f und low female t male r ti (0 6 to 1) among th ir patient with chordal l sions In papillary m scl dysfunction, Shelburne et al. (1969) found a f mal t mal ati f 0 4 t 1 Taking all o tog th th ex incid nc in thi study s th imilar t that eported abov in h umati m tral gurgit tion and in rheumati m tral st nosi

T ble VIII 2 give k y to th tiology f th m tral regurg tation. Although th mitral egurgitati found n group MIS IV and MIS V w nly small o absent these group ar included f comparison. Ba t al ndocarditi w found in 4 cases 2 in group MIS I 1 in group MIS II, and 1 in group MIS IV In all cas damag to th val w p ent pri t th attack of ndocarditis In 3 as s a history f heum ti feve w s present (ase MI 5 MI 13 and MI 20) in one c mitral valvulot my had b en performed shortly bef e endocarditi occurred. Cl ed m tral valvulot my (t ble VIII 2) h d been performed in 19 pati nts (exclud ng th bov mentioned p tient who had ndocarditis) In 9 f these a systol c m rmur h d appeared o ncre ed following the valvulotomy In 4 of th cases the auscultat ry finding wer unchanged a to api al systolic murmur In the re maining 6 patients insufficient information w available as to any chang in the

Table VIII 2 Ftiological f ct r

C p	E d dl t ( )	In r ( )	V l lot my R g git ti U d h ( )	U g d k vn ( )	Rhe matic f r with t do r d ci r val l t my ( )	Oth r ses ( )	Unknown ( )	All ca s (n)	Rhe matic feve combi d
MIS I	2	2	0	1	7	0	2	14	10
MIS II	1	1	1	0	3	1	1	8	4
MIS III	0	2	1	3	0	0	1	7	5
MIS IV	1	1	0	0	0	0	3	5	2
MIS V	0	3	2	2	1	0	1	9	5
MIS I V	4	9	4	6	11	1	8	43	26

intensity of systolic murmur Among the 13 cases in which sufficient information was available regarding the intensity of the systolic murmur before and after valvulotomy 9 cases thus showed auscultatory evidence of increased regurgitation. It should however be remembered that an increased apical systolic murmur could just as well be caused by an increased cardiac output as by an increased mitral regurgitation. A certain degree of variation in the evaluation of the inten sity of the murmur must also be accepted.

Rheumatic fever w s the only known etiological factor in 11 case and the most likely cause in the above described 4 cases (in which the mitral regurgitation was judged to be unchanged after valvulotomy) Out of the total f 43 cases 26 had a history of rheumatic fever

In one case (MI 46) the r gurgitation was most probably caused by infarction of the papillary muscle (this case has been discus ed in chapter IV) In eight cases no definite cause of the mitral regurgitation could be found Rheumatic fever i still a possible etiology in th e cases a thi di ease may have a silent course

Among the 19 case which had a significant mitral regurgit tion (group MIS I II III) and in which the eti logy could be stablished with a fair degree of cer tainty th ca se wa rheumatic fever in 10 c se (53 per cent) valvulotomy in 5 cases (26 per cent) and endocarditi in 3 cases (16 per ent) In th one remain ing case another cau was pr sent (myocardial infarction)

Types of mitral regurgitation, In chapte II a description wa given of the patho-anat mical lesions and th patho-physiological mechanisms causing mitral regurgitation, However many of thes type of mitral regurgitation are uncomm n and difficult to diagnose clinically A separation into main types has been ttempted by Seltzer and Katayama (1972) who described ev n types heumatic mitral egurgitation isolated rupture of th chordae tendine e the billowing mitral valv syndrome postinfarctional mitral r gurgitation, congenital mitral regurgitation mitral regurgitati n due to bac t rial endocarditis and a miscellan ou group As thi divisi n into types appears to hav practi al advantage (p ognostic and surgical) it will be used here with some modific tions, the rit ria f which are listed below

Typ 1 Postinfarcti nal mitral egurgitation. Patients with evidence of previou myocardial infarction ith r from th anamnesis or by instrumental examination (e g dem nstr tion of pathological Q waves in the ECG or of myocardial aneurism by roentg nol gical examination) and absence of mitral egurgitation pr o to th infarct. Patients w re thus classified into this type independ nt of whether they had th papillary muscle insufficiency syndrome o papillary muscle rupture

Type 2: I olated rupture of the chorda tendineae Patients in whom symptom f mitral egurgitati n developed suddenly with the simultaneous occurrence of typical mitral regurgitation murmur and who did not belong to type 1

Typ 3 C epidal mitral regurgitation, Patients with a history of rheuma tic feve bact rial endocarditis or mitral valvulotomy and who did not be long to type 2 Furtherm re patients wer classified into this group if con comitant mitral stenosis was present.

Typ 4 Billowing mitral valve syndrome. Patients with a late systolic murmur and/or a midsystolic click, and who did not belong to type 1

Type 5: Congenital mitral regurgitation. P tients in whom other congenit

Table VIII 2 Etiological factors

Group	Endocarditis (n)	Valvulotomy (n)	Valvulotomy: Regurgitation (n)	Valvulotomy: Unknown (n)	Rheumatic fever with endocarditis or valvulotomy (n)	Other (n)	Unknown (n)	All cases (n)	Rheumatic fever combined
MIS I	2	2	0	1	7	0	2	14	10
MIS II	1	1		0	3	1	1	8	4
MIS III	0	2	1	3	0	0	1	7	5
MIS IV	1	1	0	0	0	0	3	5	2
MIS V	0	3	2	2	1	0	1	5	3
MIS I-V	4	9	4	6	11	1	8	43	26

some difficulty in doing their work if thi demanded higher degree of physical activity Class III included patients who had a m rked limitation in physical activity Undemanding activity caused discomfort Thus pati nts could not walk up to th first floor without stopping They had to rest aft walking a few hundred m ters on the level Class IV indicat s evere limitations in physical activity Not even the least exercise could be p rformed without discomfort. These pati nts could thu only walk from on room to another with discomfort and difficulty

Digitalisation and diuretic tre tm nt hav a favour ble influenc on th condition of the patients, including functional capacity and d spnoea. In eva l ating the clinical severity of a cardiac disease th se fact rs have to be taken into consideration. A clinical severity index" (CSI) was cal ul ted among these patients by adding the number of the functional lass (1 5) to th grading of diuretic therapy (1-4) (the latter was d vided into four groups of increasing intensity (table VIII-4)) and adding one if th pati nt wa digitalised and 0 if not. Thus a patient in functional class II A receiving ne th r diuretics nor digitalis preparation would have a CSI f 3 A pati nt in funct onal class III receiving 160 mg of furosemid as w ll a dig xin would have a CSI of 9 The rang of CSI i accordingly from 2 to 10

The clinical finding w re also evaluated cording to information in the case records. In case of discrepancy between ob rv the opinion of the more experienced obs rver was u ed. This system w s used in particular in evaluation of the heart auscultation, wher ttenti n wa also paid t th amount of detail available in th description.

It should be mentioned in particular th t in grading the ntensity f murmur the system of Levine (1933) w u ed, ording to which the loud st m rm has an intensity f grade 6 Differentiation betw en opening snap and third h art sound was aided by the r marks of Hultgren t al. (1968) the third heart sound being a later and lower pitched thud and the opening snap being an arlier and higher pitched snap and by phonocardi graphy

Phonocardiography w s performed using the El ma instrum nt i. e dynamic mi rophone connected to an ink j t record r[1] By thi technique systoli m rmurs were readily record d wh s diastoli murmu s were generally easi heard than recorded, this wa particularly the cas for high pitched diastolic m rmur

RESULTS AND COMMENTS

SYMPTOMS

The first sympt m am ng 9 p ti nt who had rheumati feve as th only tiol gical fact r listed n tabl VIII 3 It een that dyspnoea wa the most ommon first symptom and palp tations th next common sympt m Th interval between the occurrence of th first symptom and th examination also een in table VIII 3 A wid variation in thi int rval is s en among the patients.

Palpitati h d been noti ed in 15 p ti nt in th majority of as unrelated to exercise (t bl VIII-4) Thi symptom occurred mainly among th patients who had dominant mitral regurgitati n (group MIS I and II) Th patient who had palpitation had a gurgitant fraction (RFLVO) f 0 496 ompared t 0 269

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1) El ma Mingograph 31 with phonomicrophone o Mingograph 34 with EMT 21 phonopreamplifi and phonom roph ne El ma Schönander Solna, Sweden.

for those without palpitations: this difference was statistically significant ($p < 0.05$). Precordial pain occurred in 12 patients mainly at exercise. No correlation to the degree of mitral regurgitation was seen. Paroxysmal tachycardia did not occur in any patient. Neither was any case of persistent hoarseness met in this material. Two patients had a history of systemic emboli, one case occurred in group MIS II (case MI 08), the other in group MIS III (case MI 44). Pulmonary embolism occurred in only one case (case MI 07) belonging to group MIS II. Haemoptysis occurred in 5 patients. In 3 of these only the sputum was bloodstained (1 case belonged to group MIS II and 2 to group MIS III). In one case belonging to group MIS I the haemoptysis was minor. The last case (case MI 29) belonging to group MIS V had a major haemoptysis. The left atrial mean pressure for these 5 patients was 15, 20, 15, 19, 26 mm Hg, respectively, at the examination.

An episode of pulmonary oedema was registered in 3 cases belonging to group MIS I, II and III, respectively (case MI 16, 21 and 5). The left atrial mean pressure at the haemodynamic examination was 11, 15 and 4 mm Hg, respectively. The cardiac index was 2.2, 1.9 and 3.1 $l/min/m^2$, respectively.

The presence of dyspnoea at rest was evaluated by asking the patient how many pillows they used at night. The results are seen in table VIII 4. 10 patients had definite dyspnoea at night, 14 slight dyspnoea and 16 none. The dyspnoea at rest did not appear to be related to the degree of regurgitation. The left atrial mean pressure for the dyspnoea groups 0, +, ++ was 13.9, 11.6 and 13.6 mm Hg, respectively (n = 16, 14, 10), these numbers did not differ statistically ($p = 0.42$). The cardiac index in the same groups was 2.3, 2.6, 3.2 $l/min/m^2$, respectively; these values were also not significantly different ($p = 0.16$).

Selzer and Katayama (1972) stated that the clinical symptomatology consisted of effort dyspnoea, weakness and palpitations as the most common symptoms. The presence of effort dyspnoea was not separately evaluated in this study; shortness of breath was usually the limiting factor in the functional capacity evaluation, which will be described later. Fatigue is a vague term and present in almost every disease and is accordingly not evaluated in this study. Palpitations were also found to be a common symptom by Bentivoglio et al. (1961) (46 per cent) and by Brigden and Leatham (1953) who found that it was due to frequent extrasystoles. An alternative explanation for this symptom which was found in 8 out of the 14 patients with significant and severe mitral regurgitation (group MIS I) is the increased stroke volume. It should be mentioned that the palpitation was mainly felt at rest, possibly because in this situation attention is more easily directed to the heart.

Chest pains of almost every type were found in 27 per cent by Bentivoglio et al. (1961); this symptom has also been described by Ross et al. (1958) and Selzer and Katayama (1972) and was also found in this study. It did not have any special characteristic and did not increase in incidence with increasing regurgitation.

Systemic embolism was a rare finding in this study as it was in the studies by Bentivoglio et al. (1961) and Selzer and Katayama (1972). Coulshed et al. (1970)

found a similar incidence of embolism in p tients with mitral insuff iency (17 per cent) and in patients with mitral stenosis (19 per cent) Th latter author found that the pre ence of atrial fibrillation wa the most significant factor in the etiology of embolism but increasing age was also a significant fact r- the size of the left trial appendage however was unimportant according to these autho s.

Episode of ha moptysi have been reported in most studie of patient with mitral regurgitati n: McGregor and Zion (1955) reported an incidence of 8 per ent, Bentivoglio et al. (1961) 18 per cent, and S lzer and Katayam (1972) 16 per cent. The numbers are similar to the finding in thi study in which h moptysis occurred in 2 out of 14 patients with severe and dominant mitral regurgi tation (group MIS I) The haemoptysi was minor in all th five p ti nts in thi study with this symptom except fo one patient who had dominant mitral stenosis. Jouve et al. (1965) howev described m jo haemoptysi (> 1/2 litr) in 5 patient with pure or dominant mitral regurgitati n; th haemoptysi w s d scrib- ed recurrent, and the pr sure in the pulm nary irculation high. Bentivoglio et al. (1961) found frequently recurrent haemoptysis in only 2 out of 61 p ti nt with mitral insuff i ncy

A hist ry of pulmonary oed ma w s found in 5 out of 61 patients with mitral regurgitation by Bentivogli t al. (1961) and in 15 ut of 97 patients by Jouve et al. (1965) In thi study pulmonary oedema had occurred in 2 out of 29 p ti nt with significant mitral regurgitation; th mean left trial pressure was not high among th e p ti nts but the athet riz tion was al o arried out at a diff ent tim from that of th acut episode (f llowing whi h medi al treatm nt i likely to hav be n intensif ed)

Hoars ness h been d scribed in mitral regurgit ti n (Camishi n et al 1966 Balfour and Ayoub 1968) This sympt m which is ascribed to ompre sion of th left ecurrent laryngeal nerv betw an nlarged l ft pulm ary artery and the orta (Ari et al 1955) w s not found in thi study and m st be are in mitral in suffic ncy as it has not been d sc ibed by ith Bentivoglio et al. (1961) among th ir 65 p ti nt by S lze and Kat yama (1972) among th ir 88 p tient

FUNCTIONAL CAPACITY AND TREATMENT

Th distributi of p tients into functi nal l ses i appar nt from tabl VIII-4 No correl tion apparent betw en functional incapa ity and egurgitati n. The larg st clas II B; thi finding s p obably due to election, as th se p tients had suff cient disc mfort to be admitted to h spital; on the other hand they w re not so ill that th rough ha modynami examinati n ould not be carried out, s d scribed in chapt III and IV In the following, la I and II A will be evaluated togeth s will l ss III and IV in order t obtai uffi ient number The car diac index in l I + II A w n th v rag 2 67 l/min/m^{2} (n 8) in clas

II B 2 26 $l/min/m^2$ (n 20) and in class III + IV 2 05 $l/min/m^2$ (n 4) the averages did not differ statistically The left atrial mean pressure (LAMP) for class I + II A was 10 9 mm Hg (n 11) for II B 12 4 mm Hg (n 8) and for III and IV 15 3 mm Hg (n 8) respectively these values were also not significantly different (p 0 23) The heart volume determined roentgenologically (CVI) as described in chapter V was on the average 654 844 and 904 ml/m^2 respectively for classes I + II A (n 10) II B (n 23) and III + IV (n 7) these volumes were significantly different (p 0 02) The average ge in the above menti ned combination of classes was 36 43 and 44 years respectively these numbers were not significantly different (p 0 07) The division into functional classes thu correlated well with the heart size and showed a trend in correlation to left atrial mean pressure and cardiac index which, however was not statistically signif cant.

At the tim of catheteri tion 30 patient were digitalised (table VIII-4) Digi talisation was done uniformly among the MIS groups with the possible exception of group MIS IV where only 2 out of 5 patients received digitalis or digoxin. 16 of the patient received diuretics at the tim of he modynamic examination, as een from table VIII-4 Tho e rec iving di retics are app rently evenly distri buted among th MIS groups

The clinical severity of the h rt disea was valuated through the clinical severity index (CSI) as described in Methods thus taking the functional capa city as well as tr atment into consideration. For g oups MIS I V the average and range of CSI and number in the groups were 5 1 (6 2) 14 5 5 (7 3) 8 5 4 (7 3) 7 3 4 (6 2) 5 and 5 6 (8 3) 9 These groups were accordingly rather similar in clinical severity except f r group MIS IV It is rema kable that in the group of sev re and dominant mitral regurgitation (group MIS I) 5 patients had a everity index of 4 or less

CLINICAL FINDINGS

HEART FAILURE

Objective clinical signs of left h rt failure are dyspnoea t rest and findi gs of crepitation, dullne on percuss on and decreased respiration at the bases of the lungs on stethoscopy 30 patients did not have ny signs of dyspnoea t rest In 12 cases the h ad end of the bed had to be lightly elevated so that the patient might be free from dyspnoea. 4 of th 12 case belonged to group MIS I 2 to group MIS II, 3 to group MIS III, none to group MIS IV and 3 to group MIS V Only one patient had a more marked dyspnoea t est he belonged to group MIS I Th left atrial m an pre sure (LAMP) was 12 mm Hg on the average for the patients without dyspnoea at rest compared to 13 mm Hg for those with dyspnoea at rest. The cardiac index was similarly 2 45 and 2 32 $l/min/m^2$ on the

average respectively None of these figur differed significantly Based on pulmonary stethoscopy diagnosi of pulmonary stasis was m de in only 2 se (case MI 46 and 2) belonging t group MIS II and III r spectiv ly When the linical finding of left heart failure and the roentgenological xamination ar compared striking difference is se n, as pulmonary tasis w s found in 34 out of 42 cases by the latter method. As described in chapt r V th roentg nol gical findings f left heart failure correlated well with l ft atrial mean pressure (LAMP) If evidence f left h art failure i to be proven or disproven, roentg nological examination is t b preferred to clinical examination. A pos ible explanation f r the poor result f the clinical examinati n is that th left h rt failure am ng the patients in this material w s relatively moderat

Evaluation of right heart failure was perf rmed by m suring how far the liver re ched below th costal margin in the midclavicular lin Only in 10 case w s the live felt to be enlarged (2 o 3 fing below the ostal margin) The right trial m an pressure was 8 2 mm Hg on an averag among the p tient with enlarged liv mpared to 4 1 mm Hg n an averag among the p ti nt without enlarged liver This differenc w s significantly diff rent (p 0 002) Of the 10 case of clinical right h art failur 4 w re found in group MIS I 2 in group MIS II, 2 in group MIS III none in group MIS IV and 2 in group MIS V Thu no obvious differenc was seen in th distributi n of right heart fail re among the MIS groups with th po ible exception of group MIS IV

Cyano w seen only in seven p ti nts: One in each MIS group c pt for group MIS I where 3 se were found. The cyan sis w s slight in all cases e ept f one ca in group MIS I with mod te cyanosis.

EXAMINATION OF THE HEART INCLUDING AUSCULTATION AND PHONOCARDIOGRAPHY

A definite palpabl ictu rdi (pex be t) w noti ed in 25 s (t ble VIII 5) In the r maining 18 case t w s eith noticed that the ictu was not palpable (3 e) or no comm nt o the tu cordi w s a ailable It i seen from table VIII 5 th t bs nc of a d finit ictu cordis w ncomm n in as of d minant and seve e mitral regurgitation (group MIS I) w s the pre enc of d finit tu c rdi in case of dominant and ignif ant mitral st n sis (group MIS V) If ictu rdi annot be palp ted, th m st l t al point f th h art an still be det rmined by p rcu sion. D te mined th by perc si n r by palp tion, the m st l t ral point w in tw ses the medioclavicular lin (MCL) In 26 c ses the most l t al point w loc ted pproxim tely midw y between the medioclavicular lin and the ante or axillary lin In 15 cas s the heart eached the ant r axill ry line (AAL) Table VIII 5 shows the numb r f p tient within each MIS group in whom the h art reached th AAL *Although th left heart borde* w found t be in the AAL in half of the case with a severe and d minant mitral

Table VIII 5, Ictus and impetus c rdis

C p	D fi t ly p lp bl i tu di /T	L ft h t b rd r ching AAL n/T	I p t cordis abn rm lly t ng n/Tn
MIS I	12 14	7/14	9/13
MIS II	5/8	2/8	2/8
MIS III	3/7	3/7	3/6
MIS IV	3/5	1/5	3/5
MIS V	2/9	2/9	2/7
MIS I V	25/43 **	15/43 *	19/39 **

Tn total number

AAL the anterior axillary line

insufficiency it was also seen in cases of lesser d gree of mitral regurgit tion. The verag and range of roentgenologically determined heart volume was 993 (1880-450) 707 (1530 360) and 705 (840 570) ml/m^2 on the average for cases where the heart reached AAL the midway point between AAL and MCL and MCL respectively (n 14, 24 and 2) If the latt r two groups were combined, a signi ficant difference was found between the combined group and the first group with regard to heart volume ($p < 0$ 05)

Information on the impetus cordi (cardi impuls) was available in 39 cas s. The distribution of ca among th MIS groups is seen in table VIII 5 Although the percentage of abnormally strong impetu i seen to be large among the ses of dominant and evere mitral insufficiency it i also found if th mitral regurgi tation is les pronounced. The pre nc of an abnormal impetus cordis thus doe not prove that th patient has a significant mitral regurgitation, possibly becau other factor than the stroke volume d termine wh ther impetu cordis i felt ab- normally strong and diffuse e g the body build, the amount of adipose tissu and the agittal diamet of the chest (Dressler 1950) A very diffuse or strong impetu ordi was found in 3 p tients all bel nging to group MIS I Although thi number is very small, it doe indicat that a very diffuse or strong impetu ordis i associated with a sev e mitral regurgit ti n.

Tabl VIII-6 Distribution f patients according to int nsity of systolic m rmurs,

G p	Int ity f y t li u rm (g d s)[x] 1	2	3	4	5	1 5
			n	n		n
MIS I	0	0	1	9	4	14
MIS II	0	0	5	3	0	8
MIS III	0	0	5	2	0	7
MIS IV	0	0	2	2	1	5
MIS V	3	1	4	0	1	9
MIS I V	3	1	17	16	6	43

) A di g L i 1933

Table VIII 7 Distributi n f p tients accordi g to characteristic of diastolic murmur

G p	L ng d mbli g	Sh rt d p t di t	N t p cl fi d	M di t m rm r	Pr syst mp t	I t nsity (in g d) 1	2	3	Di tolic f mi ment
MIS I	8	2	1	3	1	6	5	0	2
MIS II	4	0	1	3	0	4	1	0	0
MIS III	7	0	0	0	1	2	5	0	0
MIS IV	3	0	1	1	1	2	1	1	0
MIS V	9	0	0	0	5	2	5	2	4
MIS I V	31	2	3	7	8	16	17	3	6

) A di g t L (n 1933

A systoli murmur wa heard in 40 out of 43 cas s Table VIII 6 sh ws the intensity of the murmur It is seen that all patients with a signifi ant mitral regurgitation also had a systolic murmur at the apex and that the 3 pati nts without a systolic murmur did not have a signific nt mitral regurgitation. In this study the intensity of the systolic apical murm r alone did not help gre tly in evaluating the degree of mitral regurgitation. The systolic murm adiated to th left axilla in 38 case and to the l ft sternal bord r in 30 es. Only in 5 case did the murmur radiate to the neck, but in 9 cases the murmur radiated to the l ft side of the posterior part of the thorax. In 2 ca radiation to th right ide f the back was noticed (c se MI 15 and 31) in cas MI 15 rupture of th chordae tendi ne e had occurred In all cases the systolic m rmur had its maximum int nsity at the apex. Systolic fremissem nt wa only felt in 3 c ses belonging to group MIS I, II and IV respectively The murmur w s regarded s diffus in 33 cases only in 6 ca es was th murmur regarded as locali ed n of these cas s belonged to group MIS II two to group MIS III and three t group MIS V The systolic murmur wa of a blowing type in 30 ses in one case t was harsh, in 3 c se the murmur had blowing as well as harsh qualities. In only on case had the murmur a musical quality Th systolic m rmur w f lt to be of constant, even int nsity throughout systole in 31 c se and in 7 case appeared to be f a cr sc nd -decr scend type

Th diastoli murmurs are d scribed in table VIII 7 It i seen that the typical murmur of mitral stenosis did not exclude a significant mitral regurgitation. The only two cas s with a sh rt proto-diastolic murmur occurred am ng the pati nt with th m st severe egurgitati n (group MIS I) Among th 29 p ti nt with significant mitral regurgitation, only 6 did not have a di stolic murmur It s in t esting to not that diastolic fremissement occurred only among the patients with the m st evere mitral regurgitation and th most evere m tral stenosis H wev grade 3 di stoli murm occurred only 1 p ti nt with insignificant mitral r gurgitati n (group MIS IV and V)

In table VIII 8 the int nsity of th systolic and diastoli murmurs has been ompared for ach p tient by subtr ting th int nsity grad of th diastoli mur m r from th t f th systolic murmur The m jor ty of patient enter round murmu of similar strength, l aving few pati nts in th extremes. It would ap p ar that nly neg tiv concl sions an b dr wn. If th systolic murmur i two grad m int sity than the di stol one n d minant mitral st no is i pre nt; if th di stoli m rmur i ne grade m intense than the systolic murm r a signifi ant mit al regurgitati n is not pres nt. As the numbers are small th se c ncl sions cannot claim to b prov n.

The finding in thi study egarding murmurs in mitral dis ase are similar t th finding of othe (e g the review by P l ff and Harv y (1962) and Humphri (1964)) The l t systolic murmu s described by Segal and Likoff (1964) Hancock and Cohn (1966) and Barlow et al. (1969) howev r was not found the lack f symptom in th s pati nts did not justify them being candidates

Table VIII 8 Distribution of patients according to the difference between the in tensity of the systolic and the diastoli mitral murmurs

	Diff r			i gr d s of int		ity x)				
	n	n		n	n	n	n			
Gr p	4	3	2	1	0	1	2	3	4 -3	Av
MIS I	2	1	7	4	0	0	0	0	14	2 1
MIS II	0	2	1	5	0	0	0	0	8	1 6
MIS III	0	0	0	4	3	0	0	0	7	1 3
MIS IV	1	0	1	1	1	1	0	0	5	1 2
MIS V	0	0	0	2	3	2	1	1	9	0 6
MIS I - V	3	3	9	16	7	3	1	1	43	

x) Intensity of murmur according to Levine (1933)

for haemodynami inv stigation. Th importance of the apical systolic murmur (ASM) in estimation of the signifi ance of mitral regurgitation has been evalu ted in previous studies through the findings at closed mitral valvulotomy the main factor being the regurgitant jet felt by the palpating finger Thus Logan and Turne (1953) found strong egurgitant jet in 17 c es only one of th did not have an ASM 22 patient had a grade 3-4/4 ASM, in 4 f these patient n jet was felt t all and in 5 p tients the jet was faint Abelman et al. (1953) de scribed 22 ases with n ASM 5 of the patient had a grade 1/4 r gurgitant jet and n pati nt a grad 2/4 regu gitant jet. 14 patients had a grad 3 4/6 ASM; 4 of them d d not hav any regurgitant jet and in 2 c e th jet was grade 1/4 Wood (1954) found a grade 1/4 regurgitation in 2 per c nt of patient w thout ASM. Among patient w th a gr de 3-4/4 ASM 12 per nt d d not have any regurgitation, and 18 pe ent had only gr de 1/4 regurgit tion. Mounts y and Brigden (1954) d scribed slight regurgitation in on ut f 17 ses without ASM. Schrire (1964) among 286 p tients with no ASM found 5 patient with slight e-gurgitation and 1 pati nt with severe regurgitation.

The apical diastoli murmur and particularly the relative intensity of systolic and diastoli murm s hav been the subject of much less interest than the ASM An early diastolic murmur at the pex has been described by Hultgren et al. (1968)

who regarded it as a flow murmur In the p esent study short and protodiastolic murmur was found in 2 patients both of whom belonged to group MIS I (domi nant and severe mitral regurgitati n) Similarly Möll (1968) among 19 pati nts diagnosed as having pure mitral regurgitation on h emodynamic examination, in cluding ventriculography found 4 ses with an arly di stolic m rmur A mid diastolic murmur was described in 12 out of 22 patient with pure mit al regurgi tation by P rloff and Harvey (1962) Similarly Müller (1968) in the above men ti ned study found 5 ses among 19 patients with pu mitral regurgitation. In the pre nt study 8 out of 14 patient with dominant and sev e mitral regu gita tion (group MIS I) had long and rumbling diastolic murmur (table VIII 7) In this group the intensity of th diastoli murmur was in all case grad 2 I and le than that f the systolic murmur

In conclusion, both the present and th above m ntioned studi support the view of Abelmann et al (1953) that in mitral valve di se significant mitral re gurgitati n i unlikely in th b enc of a systolic murmur at the apex" Furth r m re significant mitral regurgit tion s unlik ly to be present if the di stolic apical murmur i loud r than th systoli apical murmur Abelmann t al (1953) furthermore sugg sted th t an apical systolic m rmur of grade 3 intensity or loude in a patient with mitral st nosis sugg sts mitral regurgitation, but does not allow an stimate of it severity" The suggesti n s well as ts limitation supported by the present study Thi study as w ll as the n by Möll (1968) demonstr te that the presence f short arly diastoli murm ndi tes signifi cant mitral egurgitation. It should finally b r m mbered as stated in chapt r III that the presence of an ap cal systoli murmur in a patient with mitral valve dis a e might also indicat tricuspid insuffici ncy and thu should not be ed to exclud pati nt from closed m tral valvulotomy but sugg st further investiga tion.

An <u>opening snap</u> was h ard r gistered by phonocardiography n 16 cas s (table VIII 9) thi sound w s found in 2 se with d minant and evere mitral regurgitati n (group MIS I) and also in 2 cas with signif ant mitral regurgit ti n without signif ant mitral stenosi (group MIS II) Thi is i contrast to th stat m nt by Wood (1954) according to which the finding of an op ning snap w an ex ellent tali man gainst th p s nce f riou mitral incompetence but in agreem nt with th findings f oth uthors: McGregor and Z on (1955) found an opening snap in 62 p ent f pati nt with predominant gurgitation B nti vogli et al, (1961) found an nc denc of 37 per ent among th ir 65 ses of ad vanced heum ti mitral r gu gitat on and P loff and Harvey (1962) found the op ning snap in 4 out of 22 s s with pure mitral regurgit tion Nixon et al, (1960) described 12 c with both signifi ant mitral regurgitation and an open ing snap At op ati n, th anteri c sp w s found to be pliant and mobil where s th post o leaflet w shrunken and immobile It may ac ordingly be oncl ded that the p sence f an opening snap does not exclud the presenc of signif ant mitral regurgitati n.

Table VIII 9 Additional ascultatory finding

G p	Op ni g p pr s t	3 d h art s present	Q 1 in mm (0 02 se) 3	4	5	6	Lo d 1st pr sent	Ac t t d 2 P pr s nt
		n	n	n			n	n
MIS I (14)	2	6	0	6	5	3	0	8
MIS II (8)	2	0	0	2	2	4	1	5
MIS III (7)	4	0	1	2	1	2	1	3
MIS IV (5)	4	0	0	3	1	0	1	2
MIS V (9)	4	0	0	3	4	1	7	5
MIS I ▼	16	6	1	16	13	10	10	23

A third heart sound (ventricular gallop) was registered in 6 out of 43 c ses (table VIII 9) These 6 c ses all belonged to the group of evere and dominant mitral regurgitation (MIS I) Brigden and L tham (1953) d scribed the third heart sound as rarely heard or recorded in pure mitral stenosis Wood (1954) described this sound s being present in 85 per cent of th case of well dev loped mitral incompetence and in 25 per cent of mild mitral incompet nce Pe loff and Harvey (1962) found a third heart sound in 26 out of 33 patients with pur mitral regurgitation. From the limited experience of this and other studie it may a cordingly be suggested that the pr sence f a third heart sound in a se of mitral disea indicat s significant mitral regurgit tion. It should be remembe ed, how ever that a third heart sound is also an imp rtant fe tur of hypertensive and ischaemic h art disease (Nixon 1961)

A fourth h art sound (trial gallop) w regist red in only one ase (case MI 15) this patient was found t have ruptured chordae t ndineae Cohen et al (1967) regarded the presence of fourth h art sound (in pati nts with mitral regurgit tion) a clue to the diagnosis of ruptured chordae t ndinea ; the authors found thi sound in nin out of eleven p ti nt w th ruptured ch rda tendine e but not in six patients with cuspidal mitral regurgitation. Sel e and K tayam (1972) howeve found only a fourth heart sound in 14 ase among 65 c ses with rupture f the chord e t ndin e a fourth h art sound was f und in 3 c se am ng 61 cases f heum tic valvular mitral regu gitation. It should be m ntioned, however that a fourth heart sound does not occur nly in mitral regurgitation, but also in cute myocardial infarction, angina p ct ris hypertension and aortic stenosis (Bethell and Nix n 1973)

A loud first heart sound at th apex wa heard in 10 c s (table VIII 9) 7 of the e patient belonged to the group of d minant mitral st nosi the othe three c ses occur ed with n se in ach of th othe MIS group except in group MIS I. Wood (1954) d scribed an ac entuated first heart sound in all 200 c ses of pure mitral stenosi and in 27 out f 100 ca of pure mitral r gurgitation; the sound among th latt r a wa d scribed as being of grad 1 2/4 and the on- cl sion w s th t loud first heart ound s ex ellent evidence f mitral stenosis but giv littl indic tio of t degr its pre nce i a talisman gainst serious m tral in mpet nc Goodwin et al (1955) described an co ntuated first heart ound in 7 pati nt n whom mitral st no i with important mitral incompet nc w diagnosed clinically The diagnosis was confirmed at operation for correc ti n f th l si n Th se author further remarked that a soft first sound had not be n notabl finding in the 10 p t e ts p esented h re wh had signifi cant stenos in ddition to incompetenc McGrego and Zion (1955) found an incre sed fi st h art sound in 33 per ent of ca s with predominant mitral re gurgitati n Benti glio et al (1961) d scribed a high pitched and sharp first h art sound in 28 p nt of ases with advanced mitral regurgitation. P loff and H rvey (1962) found slightly to moder tely increased first heart sound among 4 out of 33 pure mitral regurgitation ases Thus in mitral disease the presenc

of an accentuated first heart sound does not indicate that mitral regurgitation is absent or insignificant

The interval between the onset of the QRS complex in the electrocardiogram and the first heart sound at the apex (Q 1 interval) is also listed in table VIII 9 No obvious relation to the degree f mitral regurgitation was seen. McGregor and Zion (1958) found a Q 1 interval in patients with mitral stenosis of 0 07 sec (range 0 04 to 0 10 sec) compared to 0 08 sec (range 0 06 to 0 11 sec) in patients with mitral regurgitation. Perloff and Harvey (1962) found the Q 1 interval to be 0 058 sec with a range of 0 045 to 0 070 sec in mitral regurgitation. Considering the exactness of the examination and the range of the reported values in this and the above mentioned studies the Q 1 interval has little value in predicting whether mitral regurgitation or stenosis is dominant.

An acc ntuated econd heart sound ov r the pulmonary area was noticed in 23 cases (table VIII 9) This did not appear to be related to the degree of mitral regurgitation. The pulmonary artery systolic pressure was 45 mm Hg for those patient with an accentu ted pulmonary rtery pressure c mpared to 44 mm Hg for those patients where an accentuated second heart sound was not noticed This difference was not statistically significant (p 0 86) This lack of correlation may possibly be explained by the fact that the intensity of the second sound was not graded and that some patients had a decreased cardi c output which might decrease the second heart sound.

Other murmu s. In three cases (MI 1 8 and 39) a murmur ompatible with a diagnosis of aortic incompetence was heard· In none of these cases was the aortic incompetence regarded as significant. In one case (MI 44) systolic murmu was heard comp tible with a diagnosis of aortic stenosis. At catheterization a small gradient of 15 mm Hg was registered.

Othe f n i ng t physical e m n tion

The periph ral pulse w regarded as celer (rapidly rising) in three cases· two of them belonged to group MIS I and one to group MIS IV A celer pulse is accordingly not a common finding when significant mitral regurgitation is present.

Tabl VIII 10 lists th blood pressure measurements found by the cuff method. Neither the systol c the diastolic nor the pulse amplitude was related to the degree of m tral regu gitation.

COMBINATIONS OF FINDINGS INDICATING THE PRESENCE OF SIGNIFICANT MITRAL REGURGITATION

A correlation not alway tatistically signif cant has been found between the degree of mitral regurgitation and some findings described in this or the preceding chapters It would be of practical value if combinations of son e of these finding could indicate th presence of gnifi ant n itral regu gitation. Thu a good combination of findings would include few r better no patients with an

Tabl VIII 10 Blood pre su e measur ment by cuff method (mm Hg)

	Sy toli			Di t li			P l mplit d			
	AY	Ra g		A	Range		A	R	R	n
MIS I	121 1	140	100	74 6	95	60	46 4	70	32	14
MIS II	116 3	140	95	71 9	90	60	44 4	50	30	8
MIS III	117 1	140	100	72 1	80	65	45 0	60	25	7
MIS IV	1 9 0	160	110	70 0	80	60	59 0	90	40	5
MIS V	118 1	150	95	74 4	90	60	43 8	60	20	8

Table VIII 12 Evaluation of combin tion of findings suggesting absence of significant mitral regurgitation

Fi di g	RFLVO <0 10	RFLVO >0 30	T tal	RFLVO		
	n	n	n	Av	Range	
ADM ASM g d O d a l t nd	1	0	2	0 08	0 15	0 01
ADM ASM g d O d i t o di b t			0			
ADM ASM g d O nd imp t c di w k	2	0	3	0 11	0 31	0 00
ADM ASM g d O d LVE be t	3	0	3	0 10	0 31	0 00
A first so d d i t di b t	1		1	0 07		
Ac fi st ound and impetus c di weak	5	0	6	0 08	0 46	0 02
Ac first sound and LVE bsent	6	0	7	0 08	0 46	0 02
I tus ordi b ent and LVE b ent	2	0	2	0 07	0 07	0 06
Imp t di w k d LVE b t	12	7	2	0 22	0 86	0 02

ASM ap cal systolic murmur ADM apical diastolic murmur LVE left ventricular enlargement as evalu ted roentgenologically by total impression (chapter V) RFLVO d gree of mitral regurgitation (chapter II) T total Int nsity of murmurs according to Levine (1933)

SUMMARY

Among the patients with mitral insufficiency the cause of the regurgitation (when it could be established) was in order of frequency rheumatic fever valvulotomy bacterial endocarditis and other etiology. Cuspidal mitral regurgitation was the most common type of mitral regurgitation in this material. The first symptom of mitral regurgitation was dyspnoea or palpitation. The functional capacity was reduced in the majority of patients; it was remarkable however that among the patients who had severe mitral regurgitation, 29 per cent had only minor reduction in functional capacity.

In evaluation of left heart failure roentgenological examination proved to be superior to clinical examination, whe[illegible] estimation of liver size was a good indicator of right heart failure. Among the clinical findings the impetus cordi was only of limited value in determining whether mitral regurgitation was significant or not: in 4 out of 13 [illegible]s with severe mitral regurgitation the impetus cordi was not [illegible]garded as strong, and in 5 out of 12 [illegible]ses with insignificant mitral regurgitation the impetus was found to be strong. A very wide and strong impetus cordis however was found in only a few patients and they all had severe mitral regurgitation.

Only few auscultatory findings were able to identify patients with severe mitral regurgitation. All patients with short protodiastolic murmur at the apex o[illegible] ventricular gallop sound had seve[illegible] mitral regurgitation (but not all patients with a severe mitral regurgitation had these findings). A loud apical systolic murmur was present in all the patients who had severe mitral regurgitation, but also in [illegible]me patients with [illegible]significant mitral [illegible]gurgitation.

It was equally difficult to identify patients who did not have significant mitral regurgitation. However in this study significant mitral regurgitation was not found if the apical diastolic murmur was one grade louder than the systolic murmur. [illegible] Grade 2 ap[illegible]l diastolic rumbling murm[illegible] were found both in severe mitral stenosis and in severe mitral regurgitation. An opening snap was found in 2 out of 14 cases with severe mitral regurgitation and in 6 out of 15 patients with significant mitral regurgitation. A loud first sound was not found in any patient with severe mitral regurgitation, but in 2 out of 15 cases with significant, but not severe mitral regurgitation.

When a combination of clinical or other readily available findings was examined [illegible] an indicator of significant mitral regurgitation, it was found that the best indicator was the presence of a loud apical systolic murmur (grade 3 or louder or at least grade 2 louder than the apical diastolic murmur) combined with the finding by roentgenography of an enlarged left ventricle: 6 out of 17 of these patients had severe mitral regurgitation and the remaining patients had significant mitral regurgitation.

Combinations of findings indicating absence of mitral regurgitation were use

ful if one of the factors was the presence of a loud apical first sound. Thus among 7 patients who had a loud first heart sound and no left ventricular enlargem nt as determined roentgenologically only one patient had significant mitral regurgitation. In the present study however the number of patients in whom combinations of findings could be examined was small.

Summary

(See also the list of content n p 5)

INTRODUCTION The aim of this monograph is to des ibe and eval te a new method fo determination of mitral regurgitation and t relat th findings and symptoms in p tients to th d gree of mitral regurgitation determined.

CHAPTER I, Historical spect The m thods fo cardia diagnosis are review ed historically An ccount i given of th earli st description of diffe ent type f mitral regurgitation as well of th mitral insuffic ncy murmur Th hang ing evalu tion of mitral insuff ci ncy during the past hundred years i discussed Th newe m thod f diagnosi and surgi al treatm nt ar viewed with em phasi on th arli st reports

CHAPTER II, Anat my and function of th mitral valv n normal and pathological conditi s. A review i given of the normal anat my and function of the mitral valve appar tus The different type of mitral insuffici ncy are described system ti ally according to th site of th patho-anatomi al l si n; malfuncti n of the anat mically n rmal mitral valve is also described.

CHAPTER III, Det rmination of mit al regurgitati n. Previou m thods for emiquantit tiv and quantitativ d termination of m tral r gurgit tio are review ed and discu ed. Th method d scribed and examined in this study b sed on a m terial of 49 p ti nt an indic tor m thod using ^{85}Krypt n dissolved in saline Thi indicat whi h b low blood/g s partition coeff ci nt, w inf sed into th l ft ventricl through thet Sampl s wer take simultaneously from the l ft trium and syst mi artery Th r gu gitant fraction of th total left ven tricular output (RFLVO) w s alculated as th ratio betwee the krypton concen tration f th l ft trium and that of th systemic art ry rrected for the recir cul tion from th pulmonary art ry to the pulmonary veins. Th amount of this recirculatio w s examined: on the a erage the concentration in the pulmonary veins w s one tenth of that in th pulmonary art ry During infusion th krypton

concentrations were examined in the left atrium the pulmonary artery and a systemic artery a concentration plateau was reached in the left atrium and the systemic artery 6 8 minutes after the start of infusion and approximately 4 minutes later in the pulmonary artery The error in single determinations of RFLVO at the same sampling sit s was determined and found to be significant; the error in RFLVO determination, however was found to be small if 3 samples were taken at each sampling site and used for RFLVO determination. The error in RFLVO determination resulting from the site of left atrial sampling was determined by sampling at 4 different sites in the left atrium, considerable errors were found if extreme sites of sampling were used, procedures to avoid this type of error are described Similarly the error due to the site of infusion into the left ventricle was examined and found to be significant if infusion occurred into the inflow or outflow areas of the left ventricle Regurgitation determination as described here demands atrial septal puncture retrograde atheterization of the left ventri le and catheterization of an add tional systemic artery Complications to these procedures were met the main problem being that of atrial septal puncture due to the often greatly enl rged left atrium recommendations are given for the prevention of these complications

CHAPTER IV Hemodynamic findings. First the hemodynamic effects of mitral regurgitation are reviewed on the basis of animal experiments reported in the literature These experiments show that mitral regurgitation acts as a low re s stance path in parallel w th the systemic circuit, and that th r sulting, markedly increased stroke volume can be maintained with only a small increase in left atrial diastolic pre sure and myocardial oxygen consumption. The hemodynamic findings in the pre ent study are then de ribed P tients suffering from severe mitral regurgitation w re found to have a high total left ventricular output of the same magnitude as seen in large ventricular septal defects and during exercise F rward cardiac output was often, but not invariably reduced n these p tients A significant diastolic mitral pressu e gradient was not found to be incompatible with th presence of severe m tral regurgitation. The height and the descent rate of the v wave in the left atrial pressure tracing did not show a good orrel tion with the degree of m tral regu g tation, if these values were very high however significant mitral regu git tion was as rule found to be pr nt Th pulmonary resistance wa commonly but not alway found to be increased, when severe mitral regurgitation w s present

CHAPTER V Roentgenological xaminations In the majority of the patients the heart volum w s found to b increased The degr of heart enlargem nt was correlated to the regurgitant fr ction, r ght atrial mean pressure and decreasing cardiac output although th correlation coefficient wa small Left ventricular enlargement was demonstrated in slightly more than half of the cases with significant mitral regurgitation, Eval ation of left ventricular enlargement h wever

was difficult particularly in the left lateral projection. The us of the left ante rior oblique projection was found to be advantageous f this purp e as well s for evaluation of right ventricular enlargement. The left atrium w s found to be enlarged in all patients h ving significant mitral regurgitation The degree of left atrial enlargement appeared to be larger when atrial fib illation wa present cardiac output l w and left atrial mean pre sure high, only in the latt r case however was a statistically significant correl tion present. Att mpts of using one-dimensional measurements as indicator f individual h art chamber enlargement were only found useful in the case of the left atrium. Cal if ation of the mitral valve was found in 9 out of 41 cases examined by tomography· this was unrelated to the degree f mitral egurgitation. The majority of the patient with significant mitral regurgitation also had pulmonary stasis The pr senc of Kerley B line was found to be the earliest sign of pulm nary cong stion, with di latation of th upper pulmonary veins the econd most common finding A ex pected th se findings were correlated to th l ft atrial mean pressure

CHAPTER VI, Electrocardiogr phic examinations Atrial dysrythmia (fibrillation, flutter or fibrillo-flutte) occurred in half of all se and in half f th pati nts having severe mitral regurgitation. The pre ence of atrial dysrythmia was orre-lated to incr ased h art volume increased left atrial size and increased functional incapacity Only 2 patients had a frontal QRS axis of l than 30^{0} both had signi ficant mitral regurgitation. Th axis of the QRS-complex was correlated to the pul m nary artery systoli pre sure. In th group with severe mitral regurgitation 5 out of 14 patients had left ventricular hypertrophy p ttern. Th latter however w s also found among a few p tients with insignifi ant mitral regurgitation.

CHAPTER VII, Ultrasound examinati ns The maximal di stolic velocity of th anteri r m tral cusp movement (MDV) w found to orrelat with th degree of mitral stenosi but not with th d gree f mitral egurgitation. In th group of p tient with dominant and sev e mitral egurgitati n high well as very low val f MDV w re obtained, a low MDV thu did not rule out significant mitral gurgitation, but a high MDV valu app red to indi at significant mitral r gurgitati n. Similarly th total amplitude f anteri cusp movement in patient with gnif ant mitral egurgitation w found t vary fr m high t very low A rounded E point was found as frequ ntly among th p ti nt with dominant and ev e mitral regurgitati n am g tho e with d minant and signif cant mitral st nosi A t notic plat au t th E point howev w found in nly 2 out f 11 patient with d minant and ever mitral regurgitation, but in 5 out of 8 pa ti nts with d minant and significant mitral stenosi

CHAPTER VIII Clinical b rvati ns When the etiology in this m terial could be stablished the cause of ignificant mitral regurgitation w s found t be mainly rheumatic fev valvulotomy and endocarditis A female prepond rance was

found in this study similar to that reported in mitral stenosis. Six main types of mitral regurgitation are described, in this study all except a few cases had cuspi dal regurgitation. The first symptom of mitral regurgitation was found to be either dyspnoea or palpitation. To estim te the clinical severity of the heart di sease a clinical severity index was used which incorporated functional capacity as well as treatment with diuretics and digitalis it was remarkable that 5 out of 14 patients with dominant and severe mitral regurgitation h d only a low grade of clinical heart disease severity Clinical examination showed few patients to be in l ft heart failure contrary to th findings by roentgenological examination. A loud systolic murmur was not found to be a reliable sign of severe mitral regur gitation, but all patients with either a ventricular gallop sound or a short proto diastolic murmur at the apex also had significant mitral regurgitation. The pre sence of an opening snap or an accentuated first heart sound did not exclude the presence of significant mitral regurgitation; the latter however was not found if the apical diastolic murmur was at least one grade louder than the apical systo lic murmur The best combination of linical and ther readily available findings indicating significant mitral regurgitation was found to be the presence of a loud apical systoli murmur combined with roentgenologically proven definite enlarge ment of the l ft ventricle The number of p tients available for examination of combinations indicating absence of significant mitral regurgitation was relatively small; however it was noticed that if the opening snap was one of the factors in such a combination, the latter was found to be useful.

Dansk resume

(Summary in Danish)

INDLEDNING Formålet med d nne afhandling er at beskr e og vurdere en me tod til bestemmelse af regurgitationens størrelse ved mitralinsuffi iens samt at korrelere result tet af denne bestemmelse med symptomer og klini ke fund.

KAPITEL I, Hist riske persp ktiv r De diagnostiske metoder indenfor kardiologien gennemgå set fr et historisk synspunkt. Tidspunktet for den fø st kendte beskrivelse af de enkelt typer af mitralinsuffi ien omtal s De vekslende synspunkter vedrørende betydningen af rkendt mitralinsuffi iens f røres Begyndelsen til den ny æra af kirurgi k t rapi af mitralinsufficien omtales kort.

KAPITEL II. M tralklappens anatom og funktion unde normal og p tologi ke f hold, Mitralklapapparat ts normale anatomi og fysiol gi beskriv i en oversigt. D for kellige forme f mitralinsufficiens g nnemgå systematisk fter læ onens sæde endvid r be kri es malfunkti n af anat misk normal klapper

KAPITEL III B st mmel af regurgit tionens stø else ved mitralinsuff ciens Tidlig be krevne semikvantitative og kvantitative metode til bestemmel e af regurgit tionen størrels omtales og diskutere I hervær nde arbejde der omfatter 49 p tient r blev der anvendt n luftf rmig indikator (^{85}Krypton) de udmærk sig ved n l v blod/luft fordeling kv tient, såled at recirculationen g nnem lung ne var ringe Denne ndikato infunderedes i n fysiologi k salt vandsopløsning til venstre ventrikel medens d r samtidig blev taget blodprøver fra venstre trium og n art ie i det sto kredsløb via katetere Forholdet m ll m den blodmængd d r egurgitered s til v stre atrium pe minut og venstr ventrikels totale minutvolumen (RFLVO) kunn h efter beregnes som forholdet m ll m kryptonkoncentration rn i venstre atrium og i arterien; det var dog nødvendigt at korrig re disse konc ntrationer for den g nnem lungekredsløbet recircul rend kryptonmængde. Ved b st mmelse af RFLVO baseret på et enkelt sæt koncentration best mmelser var der en betydelig spredning; hvis der de imod

anvendtes 3 sæt blodprøver var nøjagtigheden acceptabel Den af prøvetagnings stedet i venstre atrium betingede unøjagtighed i RFLVO bestemmelsen vurderedes ved at sammenligne prøver fra 4 forskellige steder i atriet der fandtes betydelig unøjagtighed ved at anvende prøver nær lungevenernes indmundingssteder og nær mitralostiet. Unøjagtigheden betinget af infusionskateterets placering i venstre ventrikel vurderedes på lignende måde· hvis infusionen skete nær mitral eller aortaostiet var der betydelig unøjagtighed ved undersøgelsen. Bestemmelsen af regurgitationen (RFLVO) ved denne metode forudsætter retrograd kateterisation af venstre v ntrikel samt kateterisation af venstre atrium ved punktur af atrie septum især det sidste var undertiden vanskeligt at gennemfø e på grund af et stort venstre atrium hvorfor der opstod komplikationer til undersøgelsen. Modi fikationer i metodens pr ktiske udførelse anføres derfor

KAPITEL IV Hæmodynamiske undersøgelser De hæmodynamiske følger af mi tralinsufficiens omtales ved hjælp af refererede dyreeksperimentelle undersøgel ser Regurgitationen virker som et afløb med lav modstand parallelt med sy stemkredsløbet; det resulterend væsentligt øgede slagvolumen bevirker kun en ringe øgning af de diastoliske tryk i venstre atrium ligesom myokardiets iltopta gelse også kun øges beskedent. Blandt patienter med svær mitralinsufficiens fandt s venstre v ntrikels totale minutvolumen i herværende arbejde t være af samme størrels sorden som hos p tienter med store ventrikelseptumdefekter og som hos normale under arbejdsforsøg Det effektive minutvolumen fandtes redu ce et hos de fleste p tienter med svær mitralinsufficiens Hos mange af disse p tienter påvistes en betydel g trykforskel over mitralostiet i diastolen; dette fund kan såled s ikke bruge til at udelukke en betydende mitralinsufficie s Ved rørende trykkurven fra venstre atrium fandt s de hverken nogen overbevis nde sammenhæng mellem v takkens højde eller trykfaldet efter v takken og r gurgi tationens størrels d g havde fl rtallet af patienter med en meg t høj v tak også svær m tralinsufficiens Lungemodstanden fandtes øget ho næsten all p ti nt r med svær m tralinsuff c e s.

KAPITEL V Rønt mindersøgelse af tho ax, Hjertevolum n fandtes øget h s flertallet af pati nterne· hjert størrelsen var k rrele et til regurgitationen størrelse (RFLVO) minutvolumen og middeltrykk t højre atrium Fo stør el se af venstre ventrikel fandtes i lidt ove halvdel n af alle patienter med bety dende mitralinsuff c ens; vurd ring af venst e ventrikels fo størrel e fandtes at være vanskelig venstr sidep oj kti n, hvorimod venstre skråprojektion var velegnet til d tt fo mål såvel som til vurdering af forstørrelse af højr v ntri kel Venstre atrium fandtes forstørret hos alle p tienter· forstørrelsen var re lativt mere dtalt ho patienter med atri flimren, lavt minutvolumen og højt mid deltryk i venstre atrium kun i dste tilfælde var der dog tale om en statisti k set sikker sammenhæng Anvendelse af 1 dimensi nale mål til vurdering af d enkelte hjertekamres forstørrelse fandtes kun at være af værdi for venstre atri

ums vedkommende Forkalkning af mitralklapperne påvistes hos mindre end en fjerdedel af patienterne den var uden sammenhæng med regurgitationens størrelse (RFLVO) Lungestase fandtes hos flertallet af patienterne med betydende mitralinsufficiens Kerley's B linier var det tidligste tegn på lungestase med relativ dilatation af de øvre lungevener som det næstvigtigste tegn; en statistisk betydende korrelation fandtes mellem påvisningen af disse forandringer og middeltrykket i venstre atrium.

KAPITEL VI, Elektrokardiografiske und rsøgelser Atriel dysrytmi (flimren eller flagren) fandtes hos halvdelen af alle patienter og hos halvdelen af de patienter der havde svær mitralinsufficiens Der påvistes en sammenhæng mell m tilstedeværelse af atriel dysrytmi og hjertet volumen venstre atriums størrel e og funktionskapaciteten. Kun to patienter havde en frontal QRS akse på under 30^{0} begge patienter havde betydende mitralinsufficiens Blandt 14 patienter med svær mitralinsufficiens havd 5 et venstresidigt hypertrofimønster i ekg et; dette fandtes dog også ho nogle få p tienter med betydningsløs mitralinsufficiens.

KAPITEL VII, Ultralydsund rsøgelser Forreste mitralklaps maksimale hastighed i diastolen (MDV) fandtes korreleret til graden af mitralstenose men ikke til r gurgitationens størrelse (RFLVO); nogl patienter med svæ mitralinsufficiens havde høj MDV mens flertallet enten havde lav ell r normal MDV En lav MDV udelukker således ikke betydende mitralinsufficien hvorimod en høj MDV ynes at gør betydende mitralinsufficiens sandsynlig Afstand n mell m forreste og bageste position af forreste mitralklap fandte øg t hos nogle få patienter med svær mitralinsufficiens medens den var normal eller nedsat hos flertallet af disse patienter Et afrundet E punkt fandte ligeså hyppigt hos patienter med svær mitralinsufficiens som hos patienter med betydend mitralstenose Et pl teau sås fter E punktet i ultralydskurven hos 6 af 8 patienter med betydende mitralstenose hvorimod det kun fandt s hos 2 af 11 patienter med svær mitralinsufficiens.

KAPITEL VII Klinisk observationer I dette m teriel var gigtfeber valvulotomi og endocarditis de vigtigste årsager til betydende mitralinsufficiens, køns fordelingen var som for mitralstenose Blandt 8 hovedtyper af mitralinsufficiens var den genuin klapfligsmitralinsufficiens så langt den domin rend Det fø ste symptom på mitralinsufficiens var dyspnø eller hjertebanken. Til vurdering af hj rt sygdommens klini ke svæ hedsgrad anvendtes et særligt klinisk sværhedsgradsindex" i hvilket indgik såvel funktionskapacitet som behandling med digitalis og diuretica, vurder t på denn måde var det bemærkelsesværdigt, at 5 af 14 patient med hæmodynamisk svær mitralinsufficiens klinisk kun var l t påvi ket f der hjert sygdom. Ved stetoskopi og perkussion påvistes kun lungestase hos få pat enter i modsætning til vurdering ved røntgenunde søgelsen. Styrken af den apikal systoliske mislyd gav ikke nogen sikker vejledning i mitralinsufficiensens sværhedsgrad, derimod havd alle patienter med (ventrikulær) galoprytme

eller en kort apikal diastolisk mislyd betydende mitralinsufficiens Mitralklik og accentueret første lyd hørtes hos nogle patienter med betydende mitralinsufficiens Hvis den diastoliske apikale mislyd var kraftigere end den tilsvarende systoliske mislyd var mitralinsufficiensen af ringe betydning Den bedste kombination af kliniske fund til at angive betydende mitralinsufficiens var påvisning af såvel en forstørret venstre ventrikel (ved røntgenundersøgelse) som en kraftig systolisk mislyd ved apex Vurdering af den bedste kombination til at udelukke betydende mitralinsufficiens var vanskelig på grund af patientantallets størrelse· det var dog klart at tilstedeværelse af en accentueret første lyd måtte indgå i en sådan kombination.

Survey tables

The main finding for the individual patients are listed h e The abb eviati ns used in these tabl are those gen rally used in thi monograph (see p 220) ad ditional abbreviations are d scribed below The unit of th measurements are d scribed in th list f abbreviation unless th y are arb trary

Table S-1 Case No CL th ase number u ed in the fil of the cardio-vascu lar laboratory cas N MI is th ecutive number in the pr sent nvestigation. MIS group No. the p tient group number d scribed on p 81 Qual. th tech nical quality of the investig tion described n p 79 : 1 is optimal, 2 i accept able 3 s not acceptabl

T bl S-3 C the presenc f alc um in th mitral valve PC pulm nary con g tion (K ley B lin s) Rhythm. heart rhythm OR ther h art rhythm QRS Pat. (QRS p tt rn) abbreviations a in table VI-4 ept f r vi low voltage N normal and Q: pathological Q wave QRS Axis: th number efe to th frontal axis area No of tabl VI 5

T bl S-4 EP/ED ratio see p 140. ASM ADM gr de ac rding to Levine (1933) ADM type: R a rumbling and long, P protodiastol and sh rt. VG ventricular gallop sound. OS op ning sn p LFHS loud first heart sound.

T bl S 5 Sex. M mal F femal Rh. f heum ti fev EC: endocarditi Valv alvulot my Ict. ctu di imp impetus rdis.

Table S 1 Survey of hemodynamic findings I_1

C N CL/MI	MIS gr up N	Q 1	RFLVO	CI	SV	PAOS	MVA	GRAD	LAVP
3129/1	1	2	0 44				-	12	27
3873/2	3	2	0 15					9	26
5883/3		3	0 41			68	-	5	15
7347/4		3				55			
7430/5	4	2	0 09			68		0	38
7473/6	1	2	0 86			52		6	15
7450/7	2	2	0 46			64		5	-
6688/8	2	2	0 24			59		4	21
5078/9	1	2	0 57			68		3	16
7009/10		3	0 03			52	-		45
6757/11	1	1	0 84	1 7	190	52	5 5	11	45
4965/12	1	2	0 87	(4 6)	(1111)	68	-	8	26
4054/13	1	2	0 63	3 1	139	78	11 1	4	10
6595/14	3	2	0 48			52		8	23
6191/15	1	2	0 81	2 0	223	56		0	69
0914/16	1	1	0 87	2 1	430	57	12 2	5	15
5295/17	3	2	0 26			54		6	9
3746/18	1	2	0 63			-		5	28
4138/19	2	2	0 47	2 1	90	60	3 2	5	24
7758/20	2	2	0 26	1 9	62	65	-	0	10
7801/21	2	1	0 39	1 9	53	50	5 2	2	25
7840/22	4	2	0 06	2 7	56	66	2 7	3	9
5977/23	1	1	0 82	1 7	149	51	5 2	15	53
5226/24	5	1	0 05	2 1	35	68	1 4	9	21
7543/25	5	2	0 08			74		7	15
5837/26		3	0 27	2 2	71	63			16
3645/27	3	2	0 31	2 0	67	62	1 7	7	13
5492/28	5	2	0 06	2 2	36	64	0 9	17	29
8013/29	5	1	0 01	1 9	44	58	0 5	26	33
5068/30	4	1	0 05	3 6	78	77	4 4	3	6

T bl 9 1 (ntinued)

C N CL/MI	MIS & P N	Q 1	RFLVO	CI	SV	PAOS	MVA	GRAD	LAVP
8050/31	1	1	0 67	1 7	116	55	7 1	2	57
8042/32	2	1	0 38	2 2	80	61	2 6	5	15
8093/33	1	1	0 69	2 5	144	64	4 4	14	45
3422/34		3		2 3		64		5	12
6010/35	4	1	0 03	3 1	83	66	2 7	3	6
7664/36	4	1	0 02	3 1	68	72	3 3	4	6
6660/37	2	1	0 24	2 8	73	74		0	8
815/38	3	1	0 17	2 2	77	64	1 4	11	34
0666/39	5	1	0 02	1 9	63	62	1 5	6	29
3855/40	5	1	0 01	2 8	64	57	1 1	16	31
3756/41	5	1	0 01	1 9	43	63	0 8	11	29
8314/42	5	2	0 02	3 9	86	72	1 6	12	19
4465/43	3	1	0 16	2 2	48	61	1 7	10	27
1682/44	3	1	0 1	2 5	83	63	1 9	8	18
5061/45	1	1	0 75	1 3	140	50	3 8	7	20
8360/46	2	1	0 17	1 9	62	53		0	57
8591/47		3		2 0		64		6	14
4253/48	5	1	0 00	2 5	45	63	2 2	9	22
6322/49	1	1	0 59	2 3	99	54	4 0	7	57

Table S 2 S rvey of hemodynamic findings II

C N MIS s P

CL/MI	N	LVEDP/LVMDP	LAMP	LAVDR	PASP/PADP(PAMP)	PVR	RAMP	HR
3129/1	1	10/8	21	136	35/22 (28)		-	83
3873/2	3	8/4	18	215	63/30 (45)		1	73
5883/3		11/5	11	178	41/13 (25)		3	63
7347/4		/			28/13 (21)			
7430/5	4	18/15	21	296	41/20 (29)		9	100
7473/6	1	4/1	9		13/6 (10)		1	92
7450/7	2	9/5	15		21/10 (18)		5	65
6688/8	2	7/7	16		33/12 (22)		9	86
5078/9	1	11/7	9	464	22/9 (16)		2	64
7009/10		/3	33	340	60/24 (36)		7	122
6757/11	1	6/1	18	490	107/45 (63)	1830	7	81
4965/12	1	10/10	19	282	28/15 (20)	90	4	67
4054/13	1	4/0	5	113	18/8 (14)	260		91
6595/14	3	4/4	15	155	35/23 (29)		5	86
6191/15	1	18/9	33	800	113/46 (72)	1820	6	81
0914/16	1	7/4	11	520	32/18 (23)	300	0	65
5295/17	3	6/2	8	75	59/36 (45)		6	57
3746/18	1	14/10	16	115	33/15 (21)		9	52
4138/19	2	13/11	18	161	37/15 (24)	430	9	71
7758/20	2	8/6	12	162	20/7 (11)	340	1	74
7801/21	2	7/5	15	518	50/29 (37)	330	0	92
7840/22	4	4/3	7	25	38/19 (26)	360	6	83
5977/23	1	12/1	33	700	99/33 (56)	1110	9	118
5226/24	5	14/6	17	143	37/18 (25)	340	4	109
7543/25	5	7/5	13	305	30/18 (24)	-	0	77
5837/26		6/5	11	182	38/15 (23)	410	5	67
3645/27	3	7/1		80	39/18 (29)	280	2	70
5492/28	5	2/0	19	168	32/16 (23)	330	6	94
8013/29	5	3/ 4	26	61	77/34 (49)	1200	2	73
5068/30	4	/ 2	3	107	17/10 (13)		1	86

Tabl 9 2 (ntinued)

C N CL/MI	MIS g P N	LVEDP/LVMDP	LAMP	LAVDR	PASP/PADP(PAMP)	PVR	RAMP	HR
8050/31	1	15/12	26	733	38/20 (37)	320	8	79
8042/32	2	7/3	11	110	38/15 (26)	440	6	72
8093/33	1	9/5	28	276	54/21 (35)	190	6	87
3422/34		10/2	8	29	24/6 (15)	420	4	71
6010/35	4	4/1	5	20	27/6 (16)	180	1	63
7664/36	4	4/3	4	99	29/12 (19)	150	4	75
6660/37	2	10/7	6	184	20/7 (14)	230	1	75
7815/38	3	18/11	23	240	52/25 (38)	370	8	63
0666/39	5	13/11	23	57	50/23 (31)		9	60
3855/40	5	6/5	26	94	68/36 (53)	620	9	75
3756/41	5	10/8	20	97	50/16 (31)	560	2	66
8314/42	5	8/3	18	280	50/23 (37)	220	4	71
4465/43	3	7/6	20	96	49/26 (35)		6	97
1682/44	3	5/3	7	130	/ (25)		4	65
5061/45	1	8/6	16	35	28/17 (22)	250	6	70
8560/46	2	25/21	30	955	68/27 (43)	640	14	52
8591/47		7/6	12	52	36/18 (27)	400	3	78
4253/48	5	7/6	17	165	38/23 (30)	350	10	103
6322/49	1	11/5	24	910	61/30 (48)	590	9	88

Table S 3 Survey of roentgenological and electrocardiographical findings,

C N	NIS gr p								QRS	SV_1 $RV_{5\ 6}$
CL/MI	N	CVI	LVE	LAE/LAW	RVE	C	PC	Rhythm	P t /A is	(0 1 mV)
3129/1	1	1250		/18	↑		+	AFF	v/	13
3873/2	3		↑	/10	↑	0	0	SR	RVH/14	19
5883/3		590	↑	/13	?	0	0	SR	N/8	20
7347/4		730	↑	/12	0	0	0	AFI	LVH/11	44
7430/5	4	720	↑	/	?	0		SR	N/11	31
7473/6	1	780		/12	?		0	SR	LVH/8	36
7450/7	2	770		/15				AFL	N/11	24
6688/8	2	810		/		0	0	AFI	N/11	14
5078/9	1	740		/12		0		SR	LVH/12	36
7009/10		960		/13		0		AFL	LVH/12	29
6757/11	1	890		/12		0		AFL	(RVH)/14	17
4965/12	1	690	↑	/		0		SR	LVH/12	38
4054/13	1	360	0	/	0		0	SR	N/10	33
6595/14	3	1530	↑	/15	?		0	AFL	LVH/11	48
6191/15	1	970		/13		0		SR	N/4	15
0914/16	1	1160		/13	0			AFI	LVH/11	40
5295/17	3	960	↑	/	?	0		AFF	N/13	20
3746/18	1	1680	↑	/19	↑			AFL	(RVH)/13	14
4138/19	2	770	↑	/		0		AFI	N/13	22
7758/20	2	420		/	0	0	0	SR	N/9	21
7801/21	2	900		/13		0		AFL	LBBB/7	67
7840/22	4	500	↑	?/	↑	0		SR	N/12	28
5977/23	1	770		/11	↑			AFL	N/12	29
5226/24	5	620		/		0		AFI	N/11	17
7543/25	5	520	↑	/		0		SR	N/10	28
5837/26		610	0	/9		0		AFI	N/13	22
3645/27	3	660	↑	/12	↑	0		AFL	N/12	15
5492/28	5	700	↑	/		0		AFI	N/12	18
8013/29	5	610	?	/10				SR	LVH/13	34
5068/30	4	450		?/	↑	0		SR	LVH/12	59

T ble 9 3 (ontinued)

C N CL/MI	MIS E N	P	CVI	LVE	LAE/LAW	RVE	C	PC	Rhythm	QRS P t /A 1	SV1 RV5 6 (0 1 mV)
8050/31	1				/				SR	N/11	19
8042/32	2		840		/14			0	AFI	N/10	21
8093/33	1		590		/11		0		SR	N/10	22
3422/34			570		/9	↑	0	0	AFF	N/12	27
6010/35	4		560	↑	/12				AFI	(LVH)/8	34
7664/36	4		500	0	/10	0	0	0	SR	LVH/11	48
6660/37	2		520		/10		0	0	SR	N/9	18
7815/38	3				/	0			SR	RBBB/23	10
0666/39	5		790	↑	/16		0		AFI	LVH/13	81
3855/40	5		770	↑	/	↑			SR	(RVH)/13	22
3758/41	5		390	0	/9	0	0		SR	N/14	11
8314/42	5		570	↑	/11	↑	0		SR	N/14	13
4465/43	3		1300		/17				AFI	LVH/13	38
1682/44	3		1180	↑	/14		0	+	AFI	LVH/4	49
3061/45	1		1360	↑	/17		0		AFL	LVH/11	51
8560/46	2		880		/12		0		OR	Q/3	3
8591/47			880		/	↑	0	0	SR	BBB/13	24
4253/48	5		1340		/15		0		AFI	CVH/11	49
6322/49	1		470	↑	/	↑	0		AFI	N/12	17

T ble S 4 Survey of findings by ultrasound cardiography and auscultation,

C N	HIS g p		EP/ED	ASM	ADM		
CL/MI	No	MDV/TA	r tio	gr de	gr de type	VC	OS/LFHS
3129/1	1	32/2 2	0 0	3	2 R	0	/0
3873/2	3	46/1 8	0 5	3	2 R	0	/0
3883/3		/2 8		3	1	0	0/
7347/4		/	-	2	2 R	0	0/
7430/5	4	121/2 7	1 0	4	0	0	0/0
7473/6	1	338/3 4	1 0	4	0	0	0/0
7430/7	2	22/1 5	0 5	3	2 R	0	0/0
6688/8	2	39/2 3	1 0	2	1 R	0	0/0
5078/9	1	163/3 6	1 0	4	0	0	0/0
7009/10	-	-/2 3		2	2 R	0	/0
4757/11	1	-/		3	1 R		0/0
4965/12	1	28/2 0	1 0	2	1 R		/0
4054/13	1	118/3 4	1 0	3	1 P	0	0/0
6595/14	3	/	-	2	1 R	0	/0
6191/15	1	/-		4	2 P		0/0
0914/16	1	34/1 2	0 7	4	2 R	0	0/0
5293/17	3	/		2	1 R	0	0/0
3746/18	1	40/2 6	1 0	3	2 R	+	0/0
4138/19	2	54/2 2	0 6	2	1 R	0	/
7758/20	2	86/3 4	1 0	3	0	0	0/0
7801/ 1	2	/	-	2	1	0	0/0
7840/ 2	4	23/1 8	0 0	2	1	0	/0
5977/23	1	/		3	2 R		/0
5226/24	5	25/1 7	0 0	0	3 R	0	/
7543/25	5	38/1 7	1 0	2	1 R	0	0/
5837/26		-/2 2		2	2 R	0	+/0
3445/27	3	35/1 7	0 2	2	2 R	0	/0
5492/28	5	29/1 9	0 0	2	2 R	0	/0
8013/29	5	/-	-	2	2 R	0	0/
5068/30	4	80/3 5	0 4	2	3 R	0	/0

T bl S-4 (ontinued)

C No CL/MI	MIS gr P N	MDV/TA	EP/ED cl	ASM n d	ADM n d typ	VO	OS/LFNS
8050/31	1	330/3 8	1 0	3	0 -	0	0/0
8042/32	2	22/1 3	0 3	2	1 R	0	/0
8093/33	1	20/1 7	0 0	3	1 R	0	/0
3422/34		/2 1		3	2 R	0	/
6010/35	4	26/2 1	0 0	3	2 R	0	/0
7664/36	4	46/2 4	0 0	3	1 R	0	/
6660/37	2	46/3 3	1 0	3	0	0	0/0
7815/38	3	14/1 6	0 0	3	2 R	0	0/0
0666/39	5	16/2 5	0 0	4	3 R	0	/
3855/40	5	21/1 3	0 0	2	2 R	0	0/0
3736/41	5	11/1 9	0 0	0	1 R	0	/
8314/42	5	16/2 6	0 0	0	2 R	0	/
4465/43	3	52/2 2	0 3	2	2 R	0	0/
1682/44	3	14/2 6	0 0	2	2 R	0	/0
5061/45	1	15/2 2	0 0	3	1	0	0/0
8360/46	2	83/1 4	1 0	2	0	0	0/0
8591/47		/1 4		3	1	0	0/0
4253/48	5	44/2 4	0 2	1	2 R	0	/
6322/49	1	60/1 8	1 0	3	1	0	0/0

Table S 5 S rv y of clinical information,

C N	MIS g p						
CL/HI	N	Ag /	BSA	Rh f /E /val	FC CSI	Ict /Imp	BP
3129/1	1	42/M	1 66	/0/0	III 6	/	130/90
3873/2	3	49/F	1 50	/0/	III 6	/	110/75
5883/3		44/F	1 54	0/0/	III 6	/	125/65
7347/4		59/F	1 44	/0/0	IIA 4	/	130/80
7430/5	4	27/F	1 78	/ /0	I 2	/	120/60
7473/6	1	46/M	1 64	/0/0	IIB 5	/	140/70
7450/7	2	44/M	1 91	/0/0	IIB 5	/	120/75
6688/8	2	52/F	1 79	0/0/	III 7	/0	125/60
5078/9	1	32/M	1 85	/0/0	I 2	/	120/70
7009/10		36/F	1 54	0/0/0	IIB 4	/	120/95
6757/11	1	34/F	1 43	0/ /	III 8	+/	110/70
4965/12	1	23/F	2 12	/0/0	IIB 4	/0	110/65
4054/13	1	33/F	1 52	/ /0	I 2	/0	115/70
6595/14	3	39/M	1 63	/0/	IIB-7	/	100/75
6191/15	1	48/M	1 77	0/0/0	IIB 7	/	125/80
0914/16	1	41/M	1 74	/0/	IIB 6	/0	105/60
5295/17	3	34/F	1 83	0/0/0	III 6	/0	125/70
3746/18	1	41/M	1 72	/0/0	IIA 4	/	140/80
4138/19	2	42/F	1 65	/0/	IIB-5	-/0	120/70
7738/20	2	33/F	1 80	0/ /0	IIA 3	/0	95/60
7801/21	2	34/F	1 56	0/0/0	IIB-7	/	115/70
7840/22	4	40/F	1 66	0/0/0	I-4	0/0	110/70
5977/23	1	47/M	1 79	/0/	III 8	/	140/95
5226/24	5	45/F	1 68	/0/0	IIB 6	/	/-
7543/25	5	51/F	1 59	0/0/	IIB 5	0/0	95/65
5837/26		41/F	1 62	0/0/	IIB 5	0/	110/70
3645/27	3	42/F	1 60	/0/	IIB 5	/0	110/65
5492/28	5	51/F	1 48	/0/	IIB 5	/	125/85
8013/29	5	38/M	1 72	/0/	IIB 6	/0	110/90
5068/30	4	17/M	1 79	/0/0	I 2	/	115/70

T bl S 5 (timued)

C M CL/MI	MI8 & P M	Ag /	BSA	Rh f /E / 1	FC CSI	I t /imp	BP
6050/31	1	47/F	1 72	0/0/0	IIB 6	/	135/80
8042/32	2	52/F	1 66	/0/0	IIB 5	/0	140/90
8093/33	1	45/F	1 54	/0/0	IIA 3	0/0	100/65
3422/34		49/F	1 47	0/0/	IIB 7	/	110/75
6010/35	4	44 F	1 64	/0/	IIB 6	/	160/70
7664/36	4	44/F	1 61	0/0/0	IIA 3	/0	140/80
6660/37	2	23/F	1 50	/0/0	IIB 4	/0	105/70
7815/38	3	52/M	1 83	0/0/	IIA 3	-/0	115/70
0666/39	5	48/M	1 92	/0/	IIB 4	/	150/90
3855/40	5	35/F	1 69	0/0/	IV 7	/0	125/70
3746/41	5	45/F	1 55	0/0/	IIB 6	/0	105/60
8314/42	5	34/F	1 60	0/0/0	IIA 3	/0	125/75
4465/43	3	38 M	1 74	/0/	IIB 6	/	140/80
1682 44	3	52/M	1 94	/0/	IIB 5	/	120/70
5061/45	1	39/M	1 85	/0/0	IIB 5	/	110/75
8560/46		58/F	1 44	0/0/0	IV 9	/0	110/80
8591/47		46/F	1 74	/0/0	III 8	/0	125/95
4253/48	5	60/M	1 84	/0/	IIB 8	/	110/60
6322 49	1	51/F	1 57	0/0/	IIB 5	/	115/75

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Lymphatic Leukemia and Malignant Lymphoma in the Adult

A clinicopathologic study of their interrelationship

By Alf Rausing

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LYMPHATIC LEUKEMIA AND MALIGNANT LYMPHOMA IN THE ADULT

A clinicopathologic study of their interrelationship

by

Alf Rausing

Translated by L. James Brown

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CONTENTS

ABBREVIATIONS

CLL = chronic lymphatic leukemia
GER = granular endoplasmic reticulum
Hb = hemoglobin concentration
HL = malignant lymphoma histiocytic type
IF = immature foci of lymph nodes in CLL (described in text page 23)
IF n = immature foci in necropsy specimens (see text page 87)
K or L following designation of immunoglobulin class = kappa or lambda
LLD = lymphocytic malignant lymphoma diffuse
LLN = lymphocytic malignant lymphoma nodular
M/F = males/females
M-comp(onent) = monoclonal immunoglobulin component
WBC = white blood cell count or white blood cells

INTRODUCTION

This work concerns the natural history of and the relationship between various forms of lymphatic leukemia and malignant lymphoma with special reference to the following questions

1 Does the morphologic picture of the lymph nodes in chronic lymphatic leukemia (CLL) differ from that in aleukemic lymphocytic malignant lymphoma?
2 What are the leukemic manifestations of the various histologic and cytologic *forms of lymphocytic malignant lymphoma?*
3 *How do the histologic, cytologic and clinical pictures in this group of diseases* develop from the time of diagnosis to the terminal stage? Special reference is made to the development of histiocytic malignant lymphoma and Hodgkin s disease
4 Should Waldenström s macroglobulinemia be regarded as a lymphocytic malignant lymphoma and does its development resemble that of other malignant lymphocytic lesions?

Chapter I

HISTORICAL

The term leukemia was coined by Virchow who thought that lymphatic leukemia originated in the lymph nodes and assigned this form of leukemia to the group of lymphomas or lymph node tumours (77) He assumed that the process was neoplastic but that it was also systemic in that it characteristically involved the entire lymphatic system But he also described lymphatic tumours in non-lymphatic organs in this form of leukemia as well as localised tumours of lymph nodes, which he called lymphosarcomas and which were not related to leukemia but ran a progressive and frequently acute course Virchow thought that the conditions might closely resemble each other and that one could not exclude the possibility of an essential similarity between them (78) According to Virchow lymphosarcoma gradually becomes generalised like a metastasising tumour He also regarded the changes described by Hodgkin in 1832 as lymphosarcomas (24)

In 1865 Cohnheim (10) used the term pseudoleukemia to designate conditions with a leukemia-like picture of the lymph nodes without associated changes in the blood

In 1871 Billroth introduced the term malignant lymphoma (8)

In 1878 Neuman (51) assumed that all leukemic diseases, including lymphatic leukemia arose in the bone marrow an idea which was soon widely accepted

In 1893 Kundrat (31) distinguished between leukemia and "lymphosarcomatosis by their distribution and mode of growth, though they were cytologically similar According to him, leukemia was a primarily generalised systemic disease of the lymphatic system without destructive properties, while lymphosarcomatosis was an invasive tumour that could start in the lymphatic structures of various tissues, including the lymph nodes. Further he thought that the lesions tended to spread first locally and later to the lymphatics, and finally also via the blood-stream.

By the turn of the century two forms of leukemia were recognised viz. myeloid and lymphatic They were divided into acute and chronic forms

In 1903 Türk (68) claimed that though malignant lymphatic diseases have clinical and anatomic characteristics permitting precise classification of most cases, many transitional forms exist and one should regard lymphatic leukemia and lymphosarcomatosis as a family of closely related "lymphomatoses"

In 1908 Sternberg (66) introduced the term leukosarcomatosis for designating the combination of leukemia and sarcomatous lymphatic lesions, most often situated in the mediastinum The leukemia in this condition is, according to Sternberg, characterised by a larger and more immature form of cell than leukemia seen in association with diffuse disease of the lymph nodes He thought that this condition should be distinguished from lymphomatoses with leukemia Many cases of acute myeloid

leukemia with tumorous lesions have been described under the name of leukosarcomatosis Later Apitz (4) felt that leukemia and sarcomatous lymphatic tumours were fundamentally similar and showed the untenability of the term leukosarcoma tosis as used in the literature

In 1921 Webster (74) shared Türk s view but used the term lymphadenosis instead of lymphomatosis. He felt that the whole group was not of neoplastic nature

In Sweden lymphadenosis was for a long time probably the most widely used name for lymph node processes of this type based on the conception that lymphoma in lymphatic leukemia and in aleukemic lymphocytic lymphoma cannot be distinguished from one another histologically Tumours arising in tissues other than the lymph nodes and built up of cells recognisable as lymphocytic, have generally been called lymphosarcomas.

The older literature in this field is difficult to analyse because all lymphatic tumours (and often infectious lymphatic hyperplasia) have been included within the term lymphosarcoma. The problem complex was intimately associated with tuber culosis. Moreover myeloblastic leukemia was often included in series of lymphatic leukemia, and chloroma was often regarded as belonging to malignant lymphoma.

From the beginning of the 20th century it was possible to distinguish Hodgkin s disease from "non-Hodgkin" lymphomas (57) The 1920s and 1930s witnessed a tendency to a differentiation between tumours of the lymph nodes. The large cell and anaplastic variants of such tumours were often referred to as reticulum cell sar coma, due particularly to Roulet s work (60) This form of growth was most often not leukemic. From about 1930 clearly lymphocytic tumours were most often referred to in Scandinavia as lymphadenosis or lymphocytic lymphosarcoma while the term reticulum cell sarcoma was used for a wide variety of lesions of the lymph nodes whose definitions varied geographically and from time to time The term aleukemic reticulosis was coined by Letterer in 1924 (38) and has been used to de signate various less well defined conditions (see discussion in 35) Brill, Baehr and Rosenthal in 1925 (9) and Symmers in 1927 (67) described lymph node lesions with a follicular (nodular) structure and a relatively benign course The changes some times develop into highly malignant diffusely growing lesions. Such follicular processes were often called Brill-Symmers disease and their neoplastic nature was questioned They were often not distinguished from follicular lymphatic hyper plasia

After investigation of a large clinicopathologic material Gall and Mallory in 1942 (18) felt that malignant lymphoma is generally constant in type during its development They distinguished between lymphocytic and lymphoblastic malignant lymphoma both of which sometimes had leukemic manifestations. They suggested that the term lymphosarcoma should be omitted because it had been used with varying meaning and because lymphosarcomatosis in the sense of the term used by Kundrat is a component of lymphocytic or lymphoblastic malignant lymphoma. They believed that lymphatic leukemia and malignant lymphoma are different manifestations of one and the same disease

Rappaport s classification of lymphoma which closely resembles that of Gall and Mallory has in recent years been the one most widely used in the English spea

king countries (55) According to Rappaport all cytologic types of lymphoma can occur with nodular or diffuse growth The cytologic types are undifferentiated malignant lymphoma histiocytic malignant lymphoma and lymphocytic malignant lymphoma the last-mentioned occurring in a well differentiated and in a poorly differentiated form The classification also includes mixed histiocytic lymphocytic malignant lymphoma The lymphocytic lymphomas can according to Rappaport be associated with leukemia with a corresponding type of cell.

In 1937 Isaacs (25) used the term lymphosarcoma cell leukemia for initially aleukemic lymphosarcoma which later developed into leukemia He felt that it is possible cytologically to distinguish cells in this form of leukemia from those in genuine" lymphatic leukemia mainly by characteristics of the nucleolus

In 1942 Wiseman (79) claimed that one can distinguish chronic lymphatic leukemia from lymphosarcoma cell leukemia though both conditions may be leukemic or aleukemic According to him lymphosarcoma cell leukemia is a manifestation of a neoplastic disease in contrast with chronic lymphatic leukemia which he regarded as being of "metabolic" nature

The term "notched cell leukemia" has been used to designate a lymphatic leukemia with irregular atypical" cells seen in cases of nodular lymphomas (3)

In 1965 Schwartz et al (63) pointed out the existence of cytologic and clinical differences between CLL and lymphosarcoma cell leukemia They distinguished two forms of lymphosarcoma cell leukemia viz, chronic and acute and they thought that these should be distinguished from chronic and acute lymphatic leukemia This distinction was made on the basis of cytologic characteristics of the blood and bone marrow The picture of the lymph nodes was not described in the various groups. Schwartz et al gave a practical definition of leukemia contra lymphoma on phenomenologic grounds (involvement of the bone marrow blood picture dysfunction of the bone marrow) It is obvious that classification according to these principles may be of practical value but means that a given case will be recorded as lymphoma or leukemia depending on the hematologic findings at the time of the diagnosis and if the picture of the lymph nodes and the development of the disease are not taken in to account the classification of a given case will be arbitrary

The term lymphosarcoma cell leukemia has not been widely used Zacharski and Linman in 1969 (80) shared the view of Schwartz et al. that the condition should be distinguished from CLL because the prognosis is much poorer It is difficult to grasp whether these authors thought that it was a question of a primarily generalised systemic disease or a secondarily leukemic malignant lymphoma They disregarded the histologic features of the lymph nodes

In 1970 Schnitzer et al (6_) studied 18 cases according to the same principles as in the present work They concluded that lymphosarcoma cell leukemia is the hematologic manifestation of poorly differentiated nodular or diffuse lymphocytic malignant lymphoma

A type of lymphatic leukemia with some resemblance to CLL but with more immature cells and a poorer prognosis has been called prolymphocytic leukemia by Galton et al. (19) The lymph node pathology of this condition has not been adequately described

If Rappaport's lymphoma nomenclature is used the question of terminology is, in my opinion, different, since the word lymphosarcoma is not included and consequently also the term lymphosarcoma cell leukemia should be dropped. Rappaport wrote that well differentiated lymphocytic malignant lymphoma may be the tissue manifestation of CLL and that it is not possible to distinguish an isolated lymphoma of this type from CLL simply on the basis of the histologic picture This view is shared by several authorities e.g. Dorfman, who in 1973 (14) wrote that the best differentiated lymphocytic lymphoma is usually a tissue manifestation of CLL.

Lennert has pointed out that the picture of the lymph node in CLL may sometimes be distinguished from aleukemic lymphoma by the fact that the former has clusters of immature cells scattered among the mature ones (36)

In many recent articles, initially leukemic cases are not included in series of malignant lymphomas (e.g. 11 13,54) Dick et al. (13) believed that there is a difference between CLL and well differentiated lymphocytic malignant lymphoma but that the cytology is exactly the same However they excluded leukemic cases from their series of lymphoma.

There is a general agreement that primary aleukemic malignant lymphoma of almost all types can show a notable preterminal release of cells into the blood Some authors feel that such a release is the consequence of an overwhelming proliferation of the tumour with invasion of blood vessels and that the condition should be distinguished from leukemia in the strict sense of the word a term which should be reserved for the presence of cells in the circulation, which, so to say have a natural tendency to occur there

According to Amromin (1) lymphosarcoma cell leukemia is not leukemia at all. He thinks the condition to be similar to e.g. malignant melanoma with tumour cells in the blood. Elsewhere in Amromin's book it is stated that it may be impossible to distinguish histologically between the picture of the lymph nodes in CLL and in lymphosarcoma (2) It is difficult to understand this line of thought. Leukemic conditions with identical morphology should according to him, thus sometimes be leukemia and sometimes not.

A point which in my opinion contributes to the nosographic confusion in this field is that aleukemic malignant lymphomas are often investigated only with the aid of biopsy of the lymph nodes leukemic conditions with cytology of the bone marrow Leukemic diseases are treated by hematologists aleukemic lymph node diseases by radio-therapists. The classification of a given case will therefore depend to no little extent on the methods used by the physician who makes the diagnosis and treats the patient according to his professional background and general attitude

PRESENT INVESTIGATION This investigation concerns a series of biopsy specimens of lymph nodes showing lymphocytic malignant lymphoma with respect to the blood and bone marrow status of the patients at the time of diagnosis and during the further course of the disease The patients were followed until death and were subjected to complete necropsy The picture of the lymph nodes in clinical characteristic CLL is defined and the leukemic manifestations of other lymphocytic malignant lymphomas are described

THE CONSTANCY OF THE TYPE OF CELL AND THE MODE OF GROWTH IN THE INDIVIDUAL GROUPS OF MALIGNANT LYMPHOMAS vary according to the literature Gall and Mallory (18) claimed that the picture is most often the same during the course of the disease and in various parts of the pathologic infiltrates but they admitted that exceptions occur and that transitional forms are seen between the different groups and that such cases are seen where the process changes in morphologic character during its development Custer and Bernhard in 1948 (12) found a high frequency of such transformations. They reported a change in type in 30 40 % of all lymphatic tumours, including Hodgkin s disease Rappaport also felt that such changes were common in some groups and stated that the type of cell has a tendency to dedifferentiate during the course of the disease and that a nodular mode of growth has a tendency to become diffuse and that the mixed lymphoma group tends to become monocellular in type most often by developing into malignant lymphoma of histiocytic type Kim and Dorfmann (30) found a variation of the picture in different parts of the infiltrate in 16 % of untreated cases of non-Hodgkin s lymphoma examined with extensive biopsy at laparotomy They felt however that the constancy of the type must be regarded as high in this group of diseases. But such histologic and cytologic changes are obviously not rare in aleukemic malignant lymphomas In typical CLL such changes have been touched upon only in case reports or small series and many authors claim that they are so rare that they represent coincidence of two diseases. The transformation of chronic myeloid leukemia to myeloblastic leukemia is well known and occurs in more than every other patient with chronic myeloid leukemia and must therefore be regarded as a natural development of this disease Terminal blastic transformation in CLL is flatly denied by some authors Mørk Hansen reported terminal blastosis in 3 of his series of 189 cases of CLL (50)

As will be apparent from a later section in this book, a change in cell morphology in a more "immature" direction is common in CLL. The "new" type of proliferation however has not the tendency of the myeloblasts to pass over into the circulation and therefore the changes are rarely diagnosed intra vitam Instead of blastic leukemia the new type of proliferation tends to be some other type of malignant lymphoma

Judging from the literature Richter was the first who described a case of CLL and reticulum cell sarcoma in 1928 (58) Earlier observations of the development of large sarcomatous lesions in CLL may of course have represented the same phenomenon, but since the term reticulum cell sarcoma and the like had not been used before such cases were probably described as CLL with lymphosarcoma leukosarcoma etc. The single cases or small series reported later show that the new type of proliferation is either Hodgkin s disease or reticulum cell sarcoma most often Hodgkin s disease A coincidence of Hodgkin s disease and lymphatic leukemia was described as early as 1906 by Warthin (7) Lortholary et al reported 4 cases in 1964 and suggested that both combinations (CLL Hodgkin s disease and CLL-reticulum cell sarcoma) should be called Richter s syndrome (41) They gave a survey of earlier literature and stated that about 5 cases had been published Their survey was however not complete and including later publications I know that some 50 papers have been published on

this question All the published cases are not clearly representative of one or both of the claimed conditions, for which reason it is meaningless to review the literature in detail. Recent surveys of the literature are to be found in Vaurabourg (73) and in Long and Aisenberg (40)

To explain the coincidence of two morphologically different processes in the same tissue earlier authors have used essentially one or the other of the following theories

1 A coincidence of two unrelated diseases. Wildhack was inclined to accept this hypothesis as he said that the coincidence (CLL Hodgkin s disease) is extremely rare (76) Similar views have been presented by Lokich and Moloney (39) and by Givler (21) and several others.
2 A lymphatic leukemoid reaction in a patient with Hodgkin s disease or a sarcomatous tumour The time of onset of the two conditions usually argues against this theory because leukemia has generally been diagnosed long before the supposed onset of "reticulosis" But Marchal et al felt that such an explanation might be reasonable in their case (45)
3 The diseases differ in nature but have the same etiology Such opinions have often been published (e.g. 29 41)
4 There is a histogenetic relationship between the diseases explaining the transition of one picture to another This theory is probably the one most widely accepted (e.g. 12)
5 Treatment of the condition which appeared first has induced the second. This point has not been discussed in detail because only few cases have been reported and they have been treated in different ways.

The only opinion shared by all authors is that these changes are rare In the present material this was not the case It was therefore considered legitimate to study these transformations anatomically and clinically If CLL is a lymphocytic lymphoma similar to the aleukemic lymphocytic lymphomas, one might a priori imagine a similar development in this respect which was also found to be the case

PRESENT INVESTIGATION This paper reports a series with detailed histologic post mortem examination at which sarcomatous changes of the type described above are often revealed in CLL. As far as I know no such investigation has been published before presumably because only few tissue blocks are generally examined and focal changes are therefore readily missed

WALDENSTRÖM'S MACROGLOBULINEMIA (see 69 70 71) is difficult to classify The clinical picture is often dominated by symptoms due to the macroglobulin in the circulation and by unspecific symptoms such as fatigue and loss of body weight Surveys of various aspects of the disease have been published by McCallister et al (47) Martin (46) and by Mac Kenzie and Fudenberg (43) and others. Enlargement of lymph nodes or the spleen suggesting lymphoproliferative disease is by no means a regular finding But infiltration of the bone marrow by lymphatic cells is the rule and it is widely accepted that the anatomic basis of the disease is infiltration by lymphatic cells, the extent and site of the infiltration varying as well as the cytological picture from one case to another Surveys of the morphologic changes in macroglobulinemia have been published by Zollinger (81) Dutcher and Fahey (16)

Le Beaux and Ganter (33) Harrison (23) Rywlin et al (61) and others. The changes in the bone marrow are the most constant findings and consist of infiltration, often diffuse sometimes focal of lymphocytes, plasma cells and transitional forms (59) Mast cells are often abundant Histiocytes are usually increased in number and often contain abundant iron pigment These forms of cells are usually those which constitute the extramedullary infiltrates, if any The picture of the lymph nodes in characteristic cases resembles that seen in lymphocytic malignant lymphoma but the infiltration is less dense and the changes are not obligatory Several variants of this "classical" cytological picture are found Sometimes the picture of the bone marrow is entirely plasmocellular and resembles that seen in myeloma Sometimes the picture cannot be distinguished from that of CLL, and even clinically the condition may resemble CLL (26) Dutcher and Fahey (16) described PAS-positive inclusions in nuclei or cytoplasm but such inclusions are not obligatory and can be seen also in other diseases and in reactive conditions (see e.g 23) Many authors series contain cases, which, according to their descriptions should be regarded as "reticulum cell sarcoma" (82 with survey of the literature) or Hodgkin s disease (43) or *sometimes lymphatic lesions of the type "lymphosarcoma" (43 and others) which* may be osteolytic (e.g. 75) These cases may also be clinically more "malignant" than others and thus behave like the morphologic entity in question and some authors regard the macroglobulinemia in such cases as secondary" to malignant lymphoma and as some disease other than classical Waldenström s macroglobulinemia The problem is thus briefly whether it is a question of macroglobulinemia with malignant lymphoma or malignant lymphoma with macroglobulinemia The untenability of a primary and a secondary form in this sense has been pointed out by Mac Kenzie and Fudenberg, who reported cases which began as a primary form and afterwards became more malignant (43) They felt that it might be a question of a proliferation of immunoglobulin-producing cells that can vary from an entirely benign disease to rapidly progressive lymphoma. Similar views were presented by Rywlin et al (61) The problem is complicated further by the fact that many malignant lymphomas and lymphatic leukemias *can have an M-component of macroglobulin nature* without clinical evidence of Waldenström s macroglobulinemia (see e.g. 49) and as has been shown by e.g Stein et al. (65) tumour tissue from various lymphomas can sometimes contain abundant immunoglobulins usually of type IgM These authors therefore deny the existence of macroglobulinemia as a pathologic entity and regard the condition rather as IgM-secreting lymphoma of varying types. Such an assumption is however partly refuted by the findings by Mac Kenzie and Fudenberg who studied tumours, histologically resembling "lymphosarcoma and Hodgkin s disease" from patients with macroglobulinemia (43) Using the immunofluorescence technique they found no production of IgM in tumour tissue but they did find it in plasma cell-like elements in the bone marrow Similar findings have been reported by Palutke and Mc Donald (5_) in cases of poorly differentiated lymphocytic lymphoma with macroglobulinemia

PRESENT INVESTIGATION *In my opinion macroglobulinemia is a low-grade* malignant lymphoproliferative disease closely related to other low-grade lymphatic

malignant diseases such as CLL. Like this condition, macroglobulinemia has a tendency to progress and to develop a more malignant histologic and clinical picture The morphologic appearance and the degree of clinical aggressiveness of a given case thus depend on the stage in which the disease is first seen. It is possible that the cells, when developing in this manner assume tumour forming properties and loose the capacity of macroglobulin production.

To test this hypothesis and to define the morphologic picture in cases diagnosed clinically as macroglobulinemia I examined all cases of the disease investigated post mortem in the same way as cases of CLL and aleukemic lymphocytic lymphoma Though the material was small, it was felt that it deserved publication because only few series of macroglobulinemia with extensive routine post mortem examination are on record

Chapter 2

INTRODUCTORY REMARKS ON LYMPHOMA NOMENCLATURE

The classification of malignant lymphoma has as pointed out in a previous section, been the subject of intense debate No classification system has hitherto been universally accepted for any length of time and it is obviously difficult to find descriptive definitions to standardise the criteria for a diagnosis.

For a long time the most widely used nomenclature was based on the terms lymphosarcoma and reticulum cell sarcoma These names have been used with such different meanings that they are now confusing In recent years Rappaport s nomenclature has been used most in English-speaking countries (55) It is clinically valuable and terminologically simple It is based on the histologic arrangement of the cells, diffuse or nodular and on the degree of differentiation of the cells and their assumed cytogenesis In the present investigation lymph node tumours with initially clearly lymphocytic character and their relation to lymphatic leukemia were studied The picture of the lymph nodes in CLL is believed by Rappaport to reflect one type of malignant lymphoma One of the questions posed in the present investigation was whether the picture of the lymph nodes in CLL differs from that of non-leukemic lymphoma Since this was found to be the case it was not possible to group the appearances of the lymph nodes according to a classification of lymphomas, where CLL is grouped together with some other form of lymphoma It is generally accepted that histologically lymphoma can be divided into two groups viz. of diffuse and nodular growth This principle was therefore applied lymphocytic malignant lymphoma diffuse (LLD) and nodular (LLN) Rappaport s classification is based not only on these two types of growth of the lymphocytic lymphomas, but also on the differentiation of the cells Rappaport himself admits that the differentiation may sometimes be difficult to determine It is hazardous to apply the term differentiation to lymphatic cells because the circulating lymphocytic population morphologically well differentiated cells are not final functional stages and can develop into cells of less well differentiated appearance Morphologically less well differentiated cells may therefore be cells which have not reached or which have passed a well differentiated stage It is not yet known whether "poorly differentiated lymphoma cells should be regarded as representing the one or the other stage of the life-cycle of the lymphocytes These cells are abnormal and it is not known whether their life-cycle is the same as that of normal cells To describe lymphoid cells in this connection I decided to replace the term differentiation by the terms maturity and atypia. They are perhaps unsatisfactory but they describe different aspects which are not necessarily parallel and which cannot be distinguished by the term differentiated The same objection may be raised against maturity as against differentiation namely that an immature cell may be younger or older than a mature one The word is used descriptively in such a way as will be defined later and was chosen only as an acceptably brief term for describing the variables of cell morphology in question

The term atypia is not really satisfactory in this connection either It may be questioned whether we know the exact morphologic appearances of all stages of the life-cycle of the lymphocytes. The problem is particularly complex because the lymphatic tissue is widespread in the body and because lymphatic cells may differ in appearance from one part of the body to another Lymph nodes and other peripheral lymphoid organs contain several functional compartments which may differ morphologically It is therefore difficult to define an atypical lymphoid cell. A practical definition in the sense used in this publication is given later but it is only a "working term"

That the term differentiation as used by Rappaport is of prognostic significance in lymphocytic lymphoma appears obvious from the literature (27 and others) It may of course be used purely descriptively like mature-immature but I have found that the special aspect of the problem of lymphoma studied in this investigation namely leukemic manifestations of lymphocytic lymphoma is easier to study with the aid of 2 variables which are here called degree of atypia and degree of maturity

There are other obvious weaknesses of Rappaport s classification such as the word histiocytic for the tumour group most closely corresponding to the older group of reticulum cell sarcoma There is no evidence that the cells in these tumours have anything to do with such normal cells as are called histiocytes or reticulum cells. Tumours falling morphologically within the definitions of this group of Rappaport s may differ microscopically (and clinically) and the group may comprise several biologic entities The group of mixed histiocytic-lymphocytic lymphoma appears to suggest a mixture of 2 types of cells, which a priori appears less likely for a relatively common form of tumour

New classification systems have been formulated in an endeavour to avoid these weaknesses of Rappaport s system (Lukes and Collins, 42 Kiel-classification 20 Beard 5 Dorfman 15 Bennet et al. 6) I feel convinced that some of these systems have theoretical advantages. They are based on theories assuming that lymphoma cells have a counterpart in a certain stage of the lymphocytic life--cycle and to some extent on immunological characteristics. No large clinicopathologic studies have been presented where they have been applied and compared and until such studies are available it does not appear justified to recommend one or the other From combined biopsy and necropsy experience with malignant lymphomas and lymphatic leukemia I am convinced that it is common for these diseases to change their morphological picture during their course and that many of the pictures described in the above nomenclatures are or may sometimes be different developmental stages of the same basic disease A full understanding of their nature requires a survey of morphologic and clinical characteristics from the first symptom or sign until death. To study this aspect of disease is enormously difficult as it requires a large material of cases carefully examined on many occasions, and subjected to complete necropsy The present material is far from ideal, primarily because of its small size but to my knowledge no ideal material exists anywhere. This series is presented for what it is worth, with full acknowledgement of its defects. I have chosen a nomenclature which is as simple conventional and non-committal as possible in order to be understood by the reader whether clinician or pathologist The terms are in a general way

easy to translate into those of the above-mentioned systems however and the reader who is conversant with them is recommended to consult chapter 12 after chapter 4

Rappaport s nomenclature will be used in the present investigation but without the term differentiation Most readers probably are familiar with the definitions of lymphocytic and histiocytic types of malignant lymphoma and those desiring further details are referred to Rappaport (55) Tumours primarily classified as malignant lymphoma of undifferentiated or histiocytic type are not included in the study but since many lymphocytic tumours finally become histiocytic that term must be used In this situation these tumours are always diffuse and will therefore be referred to as "HL" thus meaning malignant lymphoma of histiocytic type with a diffuse mode of growth

The terms used are therefore

Lymphocytic malignant lymphoma diffuse (LLD)
Lymphocytic malignant lymphoma nodular (LLN)
Histiocytic malignant lymphoma (HL)

The lymphocytic lymphomas are subgrouped in a way described in chapter 4

Chapter 3

MATERIAL AND METHODS

The material consisted of adults who had died in Malmö during a 17 year period (1957 1973) Malmö is a town situated in the south of Sweden and has about 250 000 inhabitants. The town has only one general hospital, one infirmary for geriatric and chronic diseases and one mental hospital. All three hospitals are served by one institute of pathology The necropsy frequency is high. More than 95 % of all persons dying in the hospitals in the town are examined post mortem This means about 70 % of all persons dying in the town. The corresponding figure for 1957 was about 50 % The social structure of the population is such that practically all persons who die from serious chronic diseases do so in hospital the frequencies given therefore hold approximately also for the total population of the town.

All NECROPSIES were performed in a standardised way during the study period. Gross examination included intracranial structures the throat including the larynx and tonsils the mammae intrathoracic and intraabdominal organs, retroperitoneum and the pelvis as well as the testes, vessels and soft parts of the femora and the vertebral column. The lungs (at least one section from each lobe) and kidneys (at least one section from each kidney) liver spleen and heart (at least one section from each organ) were regularly examined microscopically Also sections of the vertebral bone marrow and of the prostate were usually examined. When indicated gross lesions were examined microscopically Tumours and suspected neoplastic lesions of the internal organs were always examined histologically In cases with previously known or suspected lymphoma or leukemia also the bone marrow from the femur and lymph nodes were examined microscopically Investigation of the lymph nodes usually comprised the supraclavicular mediastinal, axillary paraaortic and inguinal nodes.

Biopsy and necropsy specimens were fixed in neutral formalin and treated according to routine histotechnical methods. The sections were stained routinely with hematoxylin and eosin. The biopsy specimens from the lymph nodes were also stained according to Giemsa and with per iodic acid Schiff (PAS) and with silver impregnation for reticulin.

ASPIRATION BIOPSY SPECIMENS OF THE BONE MARROW had been obtained at the department where the patient had been cared for The material usually consisted of a sternal marrow aspirate In most cases only cytological smears had been obtained They had been stained routinely with May-Grünwald-Giemsa In most cases blood smears had also been obtained at the same time as the bone marrow specimens and were still available. The quality of the smears varied widely and many of them were diluted with blood and showed artefacts. Since histological sections were available in only a small number of cases, it could not be decided to what extent the smears were representative of the bone marrow and systematic differential counts were regarded as misleading. In those cases where percentages are given in the text

the smears were judged as representative The figures give the percentage of all nucleated bone marrow cells. 500 cells were counted

THE NECROPSY PROTOCOLS were studied to facilitate evaluation of the gross findings.

CLINICAL RECORDS were available for all cases. They varied widely regarding the details. Most cases diagnosed as CLL had been subjected to an extensive hematologic investigation at the department of internal medicine as had cases classified as malignant lymphoma and treated at the department of radiotherapy

The institute of pathology has a card index system comprising all biopsy specimens from 1957 on This index was examined for all patients.

THE PATHO-ANATOMIC NOMENCLATURE varied during the period covered by the investigation but when possible in the analysis of the cases Rappaport s lymphoma nomenclature was used with the modification described above

Infiltration outside lymph nodes is described as tumorous if grossly visible destructive lesions were found

The cases are referred to by their necropsy number A list with a diagnosis of the cases referred to is given in the end of the book

THE MICROSCOPIC ILLUSTRATIONS are arranged to follow the text as closely as possible Exceptions are made however to facilitate comparison The photomicrographs are referred to as (fig with an Arabic numeral) and figures in the text as (fig. with a Roman numeral)

DEFINITIONS The normal range of the number of white blood cells in the peripheral blood was set at 4 000 to 10 000/μl which is the normal range used at the hospital laboratory For the same reason the normal range of percentage of lymphocytes in the peripheral blood was taken as 20 45 % The term leukemia as used here is defined as follows white blood cells more than 10 000 / μl with more than 45 % lymphocytes. Here lymphocytes are to be understood as any type of lymphocytic cell also atypical and immature Objections may of course be raised against this definition and cases with other diseases can show higher percentages of such cells, but in view of the composition of the material i e firmly diagnosed lymphoproliferative diseases, it was considered acceptable

LYMPHOCYTES A mature lymphocyte is to be understood as one whose nucleus is of coarse chromatin structure and or exhibits no visible nucleolus in smears stained with May-Grünwald-Giemsa An immature lymphocyte is to be understood as a cell with lymphocytic characteristics but with clearly visible nucleolus and a less pachychromatic nucleus than that of the normal small lymphocyte The term prolymphocyte is contained within this group The cell in question is described later Cells with these characteristics were thus not called atypical unless they had the following characteristics

The term atypical lymphocyte designates a cell with structural characteristics assigning it to the lymphocytic series but with traits which do not occur in lymphocytes in normal persons in the sites and situations in question. Atypical features were generally irregularities in nuclear shape or structure and or obvious discrepancy in the nuclear/cytoplasmic relation in respect of size or maturity

The words mature and immature in the above definitions are used in their conventional morphologic sense and say nothing about my opinion of the physiological characteristics of the cell.

Blast cells are to be understood as cells without distinctly lymphocytic features and with distinct nucleoli and finely dispersed chromatin.

Some other types of cells, not conforming with these definitions, are described in the text.

The number of cells with immature features (immature lymphocytes + blast cells) were graded + to +++ in smears It is obvious that it is difficult to judge the structure of the chromatin exactly and sometimes the visibility of the nucleolus in the individual cell if the smear is of poor quality The cases were grouped according to the general impression of the smear without any attempt at differential count + only single cells with immature features (a study of some technically satisfactory smears showed that the percentage in this group was less than 5) +++ the majority of the *cells had immature features (over 50 %) ++ other cases. This classification is, of* course subjective but the margin between the groups is wide and the results are readily reproducible The cell characteristics extracted from the clinical records are given in inverted commas. "Lymphoblasts" thus indicates that the laboratory assistant had judged the cells as such and the classification is not based on cytochemical studies or the like

DATA ON SURVIVAL are calculated from the time of the clinical diagnosis or from the time when biopsy had retrospectively shown a clear picture of lymphoma. These figures are naturally of only limited value because the disease had existed for a varying time before the diagnosis.

Unless some other disease was detected at necropsy the lymphoma was regarded as the cause of death. When co-existing serious diseases were detected the probable cause of death was decided from clinical data and the findings at necropsy

THE TREATMENT given varied in type and duration from one department to another and a detailed description of the choice of therapy and the results achieved would require too much space in this presentation No distinction was made between the different types of radiotherapy From 1963 cobalt radiation was used.

THE IMMUNOGLOBULIN LEVELS were extracted from the reports of electrophoresis. The methods for determining the immunoglobulins and the normal values varied during the period in question and when exact values are given in selected cases, it is only to emphasise the development in a case or the like The terms high value and low value are to be understood as relative to the normal value used at the central laboratory at the time in question Typing of immunoglobulin components has sometimes been made in material saved from an earlier occasion (I thank Dr Anders Grubb Chemical Central Laboratory Malmö General Hospital, for help with such determinations) Sometimes no material was available for typing and in such cases the components are referred to by the terms used in the original reports.

In many cases the immunoglobulin level was investigated on several occasions during the course "Early" is to be understood as during the first half of the course roughly and "late" as the latter half of the course If the patient survived less than

one year after the diagnosis was made all examinations are regarded as "late"

THE MATERIAL WAS SELECTED IN THE FOLLOWING WAY

1 All necropsy cases of histologically or clinically diagnosed lymphatic leukemia, lymphocytic malignant lymphoma or macroglobulinemia or cases with some variant of these diagnoses were reviewed and accepted if the disease initially was preponderantly of lymphocytic type Cases with isolated soft tissue tumours without involvement of the lymph nodes, spleen tonsils or bone marrow were not included

2 All cases diagnosed as non-Hodgkin s lymphoma or lymphatic leukemia on the basis of biopsy specimens and of preponderantly lymphocytic type were examined in respect of the further development and are included irrespective of the diagnosis at necropsy provided this had been done within the period of study Aleukemic cases were thus included only if the lymphoma had initially been preponderantly of lymphocytic type but independently of maturity and atypia All cases of lymphatic leukemia were accepted irrespective of the histologic picture of the lymphoma in biopsy specimens, if any and independently of the appear ance of the necropsy specimens.

On the basis of blood and bone marrow smears some cases, originally classified as CLL, were excluded after reclassification as Sézary s disease or leukemic reticuloendotheliosis (hairy cell leukemia) No cases of these conditions are included in the material

3 Cases with a clinical diagnosis of macroglobulinemia were judged In most of them some intravital or post mortem morphologic examination had produced evidence of lymphoproliferative disease and the case was then accepted A few cases were excluded because no material revealing morphologic evidence of lymphoproliferative disease was available

In most of the cases in the series the diagnosis of malignant lymphoma or lymphatic leukemia was verified at necropsy In a few cases post mortem did not reveal any diagnostic changes but the cases are nevertheless included because of a firm clinical diagnosis. The clinical criteria for the diagnosis of CLL are difficult to determine because the patients emanated from different departments and a long period was covered but in such cases where the necropsy specimens did not show diagnostic changes the case was accepted only if intravital examination of the bone marrow or lymph nodes had produ ed a firm diagnosis

Cases where the onset was haracterised by purely blastic leukemia are not included

Two patients living outside Malmo but examined post mortem at the hospital will be discussed because they elucidate interesting aspects of the problem under discussion They are not in luded in the tables or in the frequencies, which thus represent the situation in a defined population

DESCRIPTION OF THE MATERIAL The material consisted of 160 cases examined post mortem In 80 cases mears were available from at least 1 intravital examination of the bone marrow (up to 8 examinations in some patients) At least 1 biopsy specimen of a lymph node of a ceptable technical quality was available in 41

cases and in many cases also a lymph node aspirate as well as a spleen aspirate or some other histologic or cytologic biopsy material of interest in the diagnosis of the basic disease

The age limit for the search was set to 20 years but the youngest patient was 33 years old. All the patients were Swedish citizens of Caucasian race The age and sex distribution of the entire necropsy series at the institute during the period in question is given in fig. I In 114 cases the diagnosis was CLL or lymphatic leukemia Seven cases had a diagnosis of macroglobulinemia Waldenström

Of the 2 cases from outside Malmö the diagnosis was macroglobulinemia Waldenström in one and macroglobulinemia Waldenström + CLL in the other

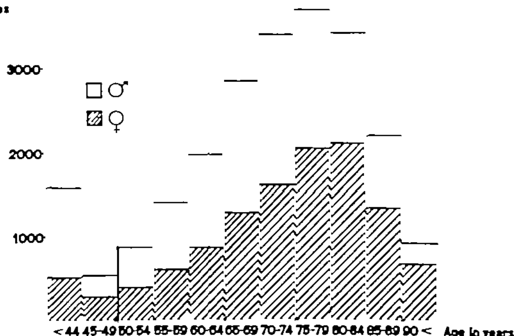


Fig. I Age and sex distribution of total necropsy series 1957 1973

DISPOSITION OF THE MATERIAL

CHAPTER 4 Study of the lymph node biopsy specimens.
Classification according to histological picture Clinical characteristics of these groups Picture of bone marrow and peripheral blood Necropsy findings. Discussion of the relation between malignant lymphoma and lymphatic leukemia.

CHAPTER 5 Study of the bone marrow aspirates.
Classification according to cytologic picture of the bone marrow Clinical characteristics of the group classified as CLL. Necropsy findings. Clinical and morphological

findings in the group with many immature cells. The group of non-leukemic lymphocytic lymphoma of the bone marrow Some illustrative case reports. Cases classified as macroglobulinemia Cases difficult to classify Discussion of the bone marrow cytologic picture and its relation to the histologic appearance of the lymph nodes.

CHAPTER 6 Necropsy series.

Classification of cases not examined with lymph node biopsy or bone marrow aspiration. Technical difficulties with necropsy specimens Some data on the necropsy material as a whole after grouping.

CHAPTER 7 Macroglobulinemia series.

Morphologic characteristics of lymph nodes bone marrow and other organs of cases clinically diagnosed as macroglobulinemia Sarcomatous transformation in this group Discussion of the possibilities of characterising this diagnosis morphologically

CHAPTER 8 Studies of the immature cells in CLL.

The correlation between immature cells in lymph nodes, bone marrow and peripheral blood The relation between the immature cells of CLL and so-called prolymphocytic leukemia The immature cells in necropsy specimens. Correlation between immature cells and monoclonal immunoglobulin components.

CHAPTER 9 Studies on sarcomatous changes in CLL and other lymphocytic lymphomas.

Frequency of development of histiocytic malignant lymphoma (HL) and Hodgkin s disease in CLL. Clinical characteristics of these cases. Topography and pathology of the lesions Development of HL in other lymphoma groups. The relation between HL and monoclonal immunoglobulin components

CHAPTER 10 Special histologic and electron microscopic investigations of immature foci of lymph nodes in CLL, and of HL in CLL.

CHAPTER 11 General discussion with special reference to the relation between CLL and HL

CHAPTER 12 Concluding remarks on the present situation regarding the nomenclature of malignant lymphoma and lymphatic leukemia

Chapter 4

THE BIOPSY SPECIMENS OF THE LYMPH NODES

I Classification according to histological picture.

The degree of differentiation in the sense of the word used by Rappaport is sometimes difficult to determine. Few lymphomas have a really homogenous picture As pointed out by Rappaport even the best differentiated tumours contain a certain amount of immature or atypical cells. In doubtful cases classification is decided by the relative amounts of the different cells. In this work it appeared important to separate atypical and immature as described earlier In the present material two main groups could be distinguished

A. Tumours with a component of cells, which in histologic sections could not be readily separated from lymphocytic cells in the normal diffuse lymphatic tissue (i.e. non-atypical cells)

B Tumours without lymphocytes of such normal appearance

In category A a consistent feature was the presence of a special type of immature cell, which was round or slightly indented and had a nuclear diameter some 50 % larger than a normal small lymphocyte The cell in question had one large generally centrally situated nucleolus. It had some slight marginal chromatin condensation and moderate amounts of cytoplasm staining moderately basophilically or grey-blue with Giemsa Three types of tumours could be separated within this category

1 The first group was dominated by small, apparently normal or almost normal lymphocytes (fig. 3) and evidently contained all clinically characteristic cases of CLL. The above mentioned immature cells were always demonstrable The group was further defined by foci, which in low magnification appeared as light areas (fig. 1) The foci varied widely in number and size but were often diffusely and evenly distributed throughout the node They generally contained a small vessel. They had no constant relation to the high endothelium,postcapillary venules, which were always present in this process. The foci were not sharply outlined against the surrounding tissue (fig.2) They contained the aforementioned immature cell in greater abundance than the surrounding tissue but the size of the majority of cells was intermediate that of such immature cells and small lymphocytes (figs. 2, 4 148) These intermediate cells had discernible nucleoli though not so large as those of the immature cells described above and a chromatin condensation and amount of cytoplasm intermediate between that of mature lymphocytes and of the large immature cells. The intermediate sized cells will hereinafter be called prolymphocytes (figs. 4-7) Their functional characteristics are not clear however In contrast with what is generally stated about CLL in the literature mitotic figures were very numerous in the above described foci and always appeared to be dividing prolymphocytes or large immature cells. The foci will henceforward be called immature foci (IF) This histologic type will be called lymphocytic malignant lymphoma, diffuse 1 (LLD-1) The IF are described in

further detail and discussed in chapters 8 10 and 11

2 A small group of tumours, consisting only of two cases, was clearly recognized where the dominating cell was the prolymphocyte described above The large immature cells were numerous. Only few mature lymphocytes were present As prolymphocytes were diffusely distributed no IF were apparent Mitotic figures were very numerous. This picture was called lymphocytic malignant lymphoma diffuse 2 (LLD 2) (figs 10 11) According to Rappaport s definitions, the picture should be called poorly differentiated but it was evident that the picture closely resembled the IF of the nodes in LLD 1 as described above

3 Tumours with a more polymorphous appearance The large immature cells were present but they were often somewhat atypical and apparently normal lymphocytes and prolymphocytes but no IF Further a certain amount of atypical lymphocytes similar to those described below were present In many cases the atypical cells outnumbered the non-atypical ones. The picture was called lymphocytic malignant lymphoma diffuse 3 (LLD-3) (figs. 20 30 37 172)

Category B had only occasional or no non-atypical cells. The atypia consisted of irregularity in the shape of the nuclei usually in the form of one or more deep clefts or general irregularity of the nuclear shape However the chromatin structure was generally coarse and gave the cells a lymphocytic appearance A small nucleolus was often seen Mitotic figures were numerous In some tumours the cell size was similar to that of the mature lymphocytes of LLD 1 in others the cells were considerably larger The range of variation in size was always wider than that of the mature cells of LLD-1 This kind of tumour was called lymphocytic malignant lymphoma diffuse 4 (LLD-4) (figs. 40 41 50-52) There was no sharp border between the small-cell and the large-cell types No IF were seen and only occasional or no prolymphocytes but a varying number of more immature and blast like cells were present They were smaller than the large immature cells of the first category and did not have their regular shape and huge nucleolus (figs 50-52) Often several smaller nucleoli were present generally situated close to the nuclear membrane These cells were similar to such as are found in the nodules of the nodular lymphomas and corresponded to the "histiocytes of Rappaport Thus the tumours in question were to some extent of Rappaport s type mixed histiocytic lymphocytic lymphoma When the lymphocytic cells markedly predominate the case should according to Rappaport be called lymphocytic as was done here It is, however evident that the classification as lymphocytic or mixed is to a certain degree arbitrary In all tumours in this group blast-like cells constituted at most about 10 % of the total number of cells and tumours with more immature cells of this type were not included in the study In some cases the blast like cells had to be searched for under high magnification for a considerable time before they could be found However no tumour was found where blast like cells were completely absent Owing to the general irregularity of the cells and the variation in size and maturity of the non-blastic component the two types of cells were not always readily recognized but a close study always revealed both types No IF were ever seen in this group but often an insignificant "cloudiness" faintly resembling nodularity (fig 49) The borderline between well differentiated and poorly differentiated tumours in Rappaport s sense of the word was

not well defined The small-cell variant is difficult to classify as either well or poorly differentiated while the large-cell type and tumours with many blast like cells would generally have been classified as poorly differentiated

The nodular lymphomas always had a cellular picture similar to that of LLD-4 and no nodular lymphoma had really normal-appearing lymphocytes within the nodules (figs. 54-58) Outside the nodules, however lymphocytic tissue with morphologically normal cells may be seen The degree of nodularity was variable As pointed out by Rappaport et al. (56) transitional forms between nodular and diffuse growth are seen (figs 53 57) Some authors, e.g. Cox et al. (11) classify as nodular any case where any nodularity at all can be demonstrated Others such as Patchefsky et al. (54) regard partially nodular cases as diffuse lymphomas. In several of my cases the nodularity was relatively insignificant in the biopsy specimen, while necropsy revealed a predominance of nodular manifestations and the former principle was therefore applied, i.e the presence of any nodularity at all classified a case as nodular Generally speaking the smaller the "histiocytic" component the poorer the demarcation of the nodules. This explains the smallness of the number of nodular lymphomas in this series, as the great majority of truly nodular tumours are of Rappaport s mixed type. It is obvious that there is no difference in kind but only in degree between the nodular cases of lymphocytic type and such as should be classified as mixed, but since this investigation concerned leukemic manifestations of lymphocytic lymphoma, the material was limited, as described above It should also be stressed that evident well demarcated nodules were needed for the classification as nodular and that the cloudiness described in LLD-4 was not regarded as nodularity A certain degree of similar cloudiness resembling nodularity may be seen in LLD-3 but never well demarcated nodules (fig. 171)

The nodular lymphomas will not be extensively studied because of the smallness of their number They were included for comparison with the diffuse types of lymphocytic lymphoma however

In the histologic classification of lymphoma technical factors are of paramount importance IF are difficult to demonstrate in poorly fixed tissue or in over-stained sections Several lymphoma biopsy specimens had to be excluded from this series as no acceptable sections could be prepared from the blocks.

The material consisted of specimens from 41 cases. The distribution of the diagnoses is given in table 1 This distribution is, of course not representative of the necropsy material because as a rule biopsy specimens were not obtained from clinically characteristic cases of CLL.

II Survival data.

The figures are given to the nearest year or month. The material is summarised in table 1

III Extent of disease at the time of diagnosis.

The simple clinical and roentgen examinations used during the major part of the period covered by the investigation did not make it possible to grade the cases according to modern principles. The findings are given in table 2.

Diagnosis	Number all (M/F)	Mean age at diagnosis, years	Mean age at death years	Mean survival after diagnosis, months	Died of lymphoma	Mean survival of those who died of lymphoma months
LLD-1	13 (10/3)	68	72	46	8/13	58
LLD-	? (M)	5? 65	53 77	16 148	2/2	
LLD-3	7 (4/3)	58	63	58	5/7	61
LLD-4	13 (10/3)	61	65	44	12/13	47
LLN	6 (?/4)	56	60	44	6/6	44
Total	41 (?8/13)					

Table 1 Lymph node biopsy series.

DIAGNOSIS NUMBER OF CASES	GENERAL ENLARGEMENT OF PERIPHERAL LYMPH NODES	A SINGLE SITE	MORE THAN ONE SITE ABOVE DIAPHRAGM	SPLEEN PALPABLE	LIVER PALPABLE	BONE MARROW EXAMINATION POSITIVE	REMARKS
LLD-1 13	9 A	3 A	1 A	4 A	2 A	8/8 A	1 ML IN NOSE
LLD 2 2	2 {1 A, 1 C}			1 A		2/2 {1 A, 1 C}	
LLD 3 7	5 {3 B, 2 C}	2 {1 B, 1 C}		2 {1 B, 1 C}	2 {1 B, 1 C}	5/6 {4 B, 1 C}	
LLD-4 13	7 {3 A, 2 B, 2 C}	4 C	1 C	4 {3 A, 1 C}	2 A	5/8 {3 A, 1 B, 1 C}	1 TONSIL ONLY (C)
LLH 6	2 C	3 {1 B, 2 C}	1 C	1 C		0/3	1 EXTRADURAL LYMPHOMA OF SPINE (C)

A >10000 WBC, >45 % LYMPHOCYTES
B <10000 WBC, >45 % LYMPHOCYTES
C <10000 WBC, <45 % LYMPHOCYTES

Table 7 Extent of disease at the time of diagnosis in lymph node biopsy series.

IV Leukemic manifestations and bone marrow findings.

The WBC and the percentage of lymphocytes in the peripheral blood at the time of diagnosis are given in table 3

Diagnosis Number of cases	WBC > 10000 Lymphocytes > 45 %	WBC < 10000 Lymphocytes > 45 %	WBC < 10000 Lymphocytes < 45 %
LLD-1 13	13		
LLD-2 2	1		1
LLD-3 7		4	3
LLD-4 13	3	3	7
LLN 6		1	5

Table 3 WBC and percentage of lymphocytes at the time of diagnosis in lymph node biopsy series

The leukemic manifestations in the various groups are described below

LLD-1 The WBC varied from 11 000 to 275 000 All cases were clinically CLL. In 8 cases the bone marrow was examined at the time of diagnosis and invariably showed heavy lymphocytic infiltration. Five of the patients had immature + 3 had ++ Of the patients with ++ 2 had also ++ in the peripheral blood 1 had +

Lymphocytic infiltration in the bone marrow was found in all 13 cases at necropsy The necropsy findings are described in a later section.

The morphology of the lymphocytes in the peripheral blood in LLD-1 was never really normal yet it was difficult to point out clearly pathological features in each individual cell The mature cell compartment always varied somewhat in size and nuclear structure (fig 5) Single immature cells could always be demonstrated in the blood in 2 cases more abundantly (++) The immature cells were cytologically identical in the blood and bone marrow They were some 50 % larger in diameter than the mature cells and had a lower nuclear/cytoplasmic ratio and the cytoplasm showed a varying degree of basophilia One or sometimes 2 nucleoli were seen (figs.5 6) The nucleus was often eccentric round or slightly indented and showed slight condensation of chromatin but the cells differed distinctly from mature lymphocytes and rarely was it difficult to decide to which group a given cell belonged These cells

correspond to the prolymphocytes described in the lymph nodes In the bone mar row an even larger cell was sometimes, though rarely met with. This cell had abun dant strongly basophilic cytoplasm sometimes with vacuoles (figs 6 143) They were rarely seen in the blood. These cells most probably correspond to the large immature cells described in the lymph nodes.

The cellular outfit of CLL is discussed further in chapters 8 10 and 11

In most patients in the group the lymphocytes in the peripheral blood were of the same size as small lymphocytes in normal persons. In 2 cases the cells were large and had fairly much cytoplasm. The mature cell content of the blood was largely the same as that in the marrow

All the cases with a low immunoglobulin level had very few plasma cells in the bone marrow One (600/65) had abundant plasma cells and high immunoglobulin values. Immature cells of the 2 above mentioned types were extremely sparse in this case

LLD-2 One case (663/58) had 52 000 WBC with 99 % immature cells of prolym- phocyte type (fig 13) Examination of the bone marrow showed dense infiltration with immature +++ (fig. 12) The patient died from the disease after 16 months and then showed diffuse myelofibrosis with lymphocytic infiltration with similar cells (fig. 14)

The other patient in this group (671/66) had a normal WBC and a normal per centage of lymphocytes at the time of diagnosis but 50 % lymphocytes in the bone marrow with half of the cells mature the other half of prolymphocytic type (fig. 17) The blood remained normal until 8 months before death, when the WBC rose abrupt ly to at most 54 000 with 90 % "atypical lymphocytes" (slide no longer available) The patient died 148 months after the diagnosis. Necropsy revealed diffuse bone mar row infiltration

The majority of the cells in both cases closely resembled the prolymphocytes in LLD-1 One case (663/58) showed a strong preponderance of these cells in both the blood and the bone marrow while the mature lymphocytes were sparse 671/66 had about 50 % of each type of cell in the bone marrow

LLD-3 The 3 aleukemic cases Only 1 patient remained without atypical cells in the blood But this patient (1140/71) only survived for 7 months. At the time of the diagnosis bone marrow examination demonstrated 30 % of lymphocytes with slight ly atypical features but few with evident nucleoli (fig. 29) WBC 4 600 lymphocytes 42 % Very rapid deterioration in spite of chemotherapy Post mortem revealed LLD plus a malignant tumour with bizarre cells resembling Hodgkin disease (figs. 31 32) This kind of tissue consisted of small foci in the lymphatic infiltrates and most of the nodes showed only LLD without Hodgkin s disease as did the marrow

One patient (855/67) had never had leukemic values, but the percentage of lym- phocytes were sometimes increased with "atypical cells" The patient died of HL 137 months after diagnosis (fig. 173) The bone marrow had been normal intra vitam and at post mortem.

One of the patients later became leukemic (1147/65) Three years after diagnosis (without treatment) this patient still had a normal WBC but 65 % lymphocytes Ra diotherapy was given and leukopenia with a varying but high percentage of lympho-

cytes developed The bone marrow 70 months after the diagnosis contained 60 % lymphocytes with many atypical but preponderantly mature cells, partly in the form of compact groups sometimes clustered around histiocytes (figs 26-28) 23 months before death (104 months after diagnosis) the WBC increased to at most 35,000 with 90 % atypical lymphocytes. The values became normal again after radiotherapy but the patient died from the disease 127 months after diagnosis. The WBC was terminally normal but necropsy revealed compact diffuse infiltration of the bone marrow

Of the 4 patients with normal WBC but a raised lymphocyte percentage only 1 remained without clearly leukemic values At the time of the diagnosis this case (1120/60) had a moderately dense diffuse bone marrow infiltration with partly atypical lymphocytes but with few immature cells (figs 33 35) while the lymph node demonstrated many large blastic forms (fig 37) There was a clear difference between the pictures of the bone marrow and the lymph nodes This patient never had more than 7 000 WBC but the lymphocytes in the peripheral blood reached 95 % (fig. 36) At necropsy 7 months after diagnosis the lymph nodes showed HL (fig. 38) while the bone marrow picture was unchanged

One case (1107/69) had at the time of diagnosis enlargement of the lymph nodes of the hilar region of the lungs, but otherwise no organ enlargement The WBC was 10 000 with 49 % lymphocytes. Examination of the bone marrow showed sparse infiltration of small-cell type with single atypical cells with deep clefts in the nucleus and immature + The diagnosis of lymphoma was regarded as uncertain and no treatment was given The WBC afterwards varied spontaneously between normal and slightly leukemic values (6 000 14 000) without any clear tendency to rise The lymphocytes of the peripheral blood generally comprised approximately 60 % of the WBC 61 months after the diagnosis the patient died of myocardial infarction without having shown any clinical signs of lymphoma and without having received any treatment The bone marrow showed focal infiltration at necropsy

Two patients (220/72 and 705/70) developed a clearly leukemic picture

220/72 had at the time of the diagnosis a WBC of 4,100 with 62 % lymphocytes, single atypical The bone marrow contained 20 % lymphocytes with moderate atypia (immature +) often in small clusters The spleen contained similar cells (fig. 39) Twenty months before death the WBC rose abruptly (from 3 600 with 44 % lymphocytes to the next examination 5 weeks later when it was 174 000 with 93 % lymphocytes) The cells in the blood showed moderate atypia but few immature forms. During corticosteroid therapy the WBC varied irregularly between this maximal value and 11 000 Forty months after diagnosis the patient died from chronic pyelonephritis. The WBC was finally ?7 000 and the bone marrow at necropsy showed focal infiltration.

Case 705/70 had a normal WBC with 72 % lymphocytes at the time of the diagnosis The bone marrow showed 88 % lymphocytes with a high percentage of atypical forms Immature ++ (figs 21 23) The peripheral blood contained mainly normal lymphocytes and only occasional atypical cells The WBC fell to subnormal level during treatment with chlorambucil. About 1 month before death WBC rose to a leukemic level with more than 95 % atypical lymphocytes (figs 24-25) At necropsy

27 months after diagnosis the bone marrow was densely and diffusely infiltrated.

The bone marrow finding in this group was characterised by mainly small lymphocytes with sparse cytoplasm. In all the cases the nuclei of a certain percentage of the cells were irregularly shaped and many showed deep clefts, which often resembled a line through the nucleus. The cleft was best seen in really thin sections (fig. 28) In many cells the structure of the chromatin was coarse but there was a varying number of more immature and blast-like cells. All varieties were seen, ranging from the coar se nuclear structure to the blast-like structure but no distinct maturity classes such as those described in LLD-1 The visibility of the nucleoli varied along a continuous scale Very often small groups of lymphoma cells were clustered around a histiocyte

LLD-4 Three cases were leukemic at diagnosis.

Case 397/59 had dense infiltration of the bone marrow with blast-like cells and the picture was at first interpreted as undifferentiated leukemia (fig. 64) The cells in the blood were however clearly lymphocytic (++) (fig. 65) The highest WBC was 99,000 At necropsy 23 months later the bone marrow was diffusely infiltrated

Case 451/61 remained leukemic during the entire course of 27 months. The bone marrow at the time of the diagnosis had shown moderately dense infiltration with large cells of a fairly coarse nuclear structure and immature ++ (fig. 43) Cleft nuclei were less common. The cells in the blood were identical. Necropsy showed diffuse infiltration in the marrow

Case 963/66 showed a successively rising WBC (20 000 60,000) with atypical lymphocytes (figs. 47 48) The bone marrow contained 60 % lymphocytes with preponderantly cleft nuclei and immature ++ (figs 45 46) The patient died from heart disease already after 5 months Necropsy revealed diffuse infiltration of the bone marrow

Of the 3 cases with normal WBC with a raised lymphocyte percentage 243/73 showed no infiltration in the bone marrow at the time of diagnosis (lymphocytes 52 % in blood) and the WBC never rose to leukemic level. The patient died after 19 months. Necropsy revealed only very small focal infiltrates of lymphoma in the bone-marrow

Case 619/64 had a WBC of 10 000 with 57 % lymphocytes at diagnosis. The bone marrow showed moderate infiltration (specimen no longer available) The patient survived 32 months. No values had been noted between the diagnosis and 5 months before death, when WBC was 34 000 with 85 %atypical lymphocytes (fig. 44) The bone marrow then showed dense infiltration with atypical cells and immature + Necropsy revealed focal infiltration of lymphoma

486/73 had a WBC of 7,200 with 56 % lymphocytes at the time of the diagnosis. Bone marrow examination demonstrated a moderately dense, diffuse infiltration in sections. The cells were moderately atypical (immature ++) The WBC fell to subnormal levels during radiotherapy but the lymphocytes of the blood were consistently atypical. The patient survived for 20 months. Four months before death the WBC began to rise to a maximum of 16 700 with 87 % atypical lymphocytes. Severe thrombocytopenia and anemia developed and the patient died of a generalised zoster

Seven cases were aleukemic at the time of the diagnosis. Two of them remained normal (1059/61 and 1047/63)

1059/61 survived only for 7 months and no specimens of the bone marrow were examined post mortem.

1047/63 survived for 15 months and had focal bone marrow infiltrates at necropsy

Two patients later had atypical cells in the blood without clearly leukemic values. Case 737/57 always had a normal WBC and normal percentage of lymphocytes, but consistently "atypical lymphocytes" in the peripheral blood No bone marrow examination during life

Case 535/62 had a normal bone marrow examination at the time of diagnosis The patient survived 93 months. One month before death 67 % "blasts" appeared in the blood when WBC were 8,300 At necropsy the bone marrow showed focal infiltrates

Three cases later became clearly leukemic (198/57 762/65 and 865/67)

198/57 survived 65 months. Two months before death the bone marrow aspirate (not available) was "dominated by blasts" Less than one month before death the WBC rose to a maximum of 12 200 with 29 % "lymphocytes and 40 % "blasts" Necropsy showed diffuse infiltration of the bone marrow and osteolytic tumours.

762/65 survived 126 months Examination of the bone marrow 60 months after the diagnosis showed no infiltration Three months before death the WBC rose to 195 000 with 94 % "lymphocytes" (specimen no longer available) At necropsy the bone marrow was diffusely infiltrated

865/67 survived 46 months Two months before death she developed leukemic values with at most 106 000 WBC with 93 % "lymphoblasts" Necropsy revealed diffuse infiltration of the bone marrow

LLN No patient was clearly leukemic when the diagnosis was made Only one had a raised lymphocyte percentage This case (300/65) survived for 34 months with fluctuating values of the lymphocytes, with a maximum of 59 % atypical lymphocytes (fig. 59) at a WBC of 4 600 The bone marrow was not examined at the time of diagnosis. Necropsy revealed osteolytic bone tumours (HL)

Another patient (609/69) had normal values at the time of diagnosis and the bone marrow appeared normal The percentage of lymphocytes afterwards fluctuated and reached a maximum of 50 % atypical lymphocytes when WBC was 7 800 The patient died 65 months after the diagnosis and the bone marrow then showed osteolytic HL-tumours

Two patients remained normal in the blood throughout One of them (613/66) survived only for 5 months Necropsy showed focal infiltrates in the bone marrow The other one (341/71) survived for 52 months. The bone marrow was normal <u>intra vitam</u> and at necropsy

Two of the patients showed constant leukopenia during treatment without abnormal cells in the blood Ten months before death one of them (219/73) had sparse bone marrow infiltrates (figs 60 63) and at necropsy massive diffuse infiltrates with necrosis The other 7?/73 showed no marrow infiltration <u>intra vitam</u> or post mortem

The cytologic picture in LLD-4 and in LLN was very similar and the blood cytology would not permit differentiation between LLD-4 and LLN The picture was quite different from LLD-1 or LLD-2 The demarcation towards LLD-3 was difficult Generally LLD-4 and LLN had more pronounced atypia but the border was unsharp and it is not possible to make a diagnosis of the lymph node histology from the blood picture Immature lymphocytes are seen in LLD-3 as well as in LLD-4 and in all those conditions blast cells in the blood are very rare.

A summary of the leukemic manifestations is given in table 4

Diagnosis Number of cases	Absolute lymphocytosis during some period	Leukemic values during some period	Bone marrow infiltration Diagnosis	Necropsy
LLD-1 13	13	13	8/8	13/13
LLD-2 2	2	2	2/2	2/2
LLD-3 7	6	4	5/6	6/7
LLD-4 13	10	8	5/8	12/12
LLN 6	2	0	0/3	4/6

Table 4 Summary of leukemic manifestations in lymph node biopsy series.

V Laboratory examinations.

The results of some measurements and tests are summarised in table 5 In some cases records of the examination in question were not available

Immunoglobulin levels. The findings are summarised in table 6

LLD-1 The 2 patients with high immunoglobulin values were 600/65 and 1404/67 600/65 had even 2 years later a high value which afterwards fell to subnormal level after the beginning of treatment In 1404/67 electrophoresis showed signs of activity probably because of an infected carcinoma of the urinary bladder No control examination was performed This group comprised 3 patients with M components

136/58 who also had IgG-myeloma

Diagnosis Number in group	1	2	3	4
LLD-1 13	8/12	3	1/8	7/11
LLD-2 2	1/2	0	No exam	0/1
LLD-3 7	5/7	0	0/4	1/7
LLD-4 13	5/13	1	3/5	3/13
LLN 6	4/6	0	No exam	2/6

1 Hemoglobin concentration below normal limit at diagnosis (M < 13 2g/100 ml F < 11 6g/100 ml)

2 Clinically significant hemolysis on some occasion during course

3 Coombs test positive on some occasion

4 Platelets below normal limit (150 x 10^3/µl at diagnosis)

Table 5 Laboratory examinations in lymph node biopsy series.

Diagnosis	Number of cases examined	Low	Normal	High	Comments
LLD 1	11 (8)	6 (8)	3	2	One case is excluded because of concomitant myeloma 2 cases with M-comp
LLD 2	2 (1)	(1)	1	1	
LLD 3	5 (7)	(2)	(2)	5 (3)	4 cases with M-comp
LLD-4	12 (8)	5 (4)	4 (2)	3 (2)	1 case with M-comp
LLN	5 (4)	(1)	5 (3)		1 case with M-comp

Numbers within brackets are examinations late in the course

Table 6 Immunoglobulin recordings in lymph node biopsy series.

185/63 had a small Igμ-component (0 23 gram/100 ml) in serum also present in urine

586/71 had a small IgμL in the urine (amount not determined)

LLD-2 663/58 was examined only at the time of diagnosis Normal immunoglobulin 671/66 fell successively during the disease from high to low values

LLD-3 In 1140/71 only one examination was performed and that some months before death. IgG and IgM were low Many of these cases however were remarkable because of their high immunoglobulin levels and this group had the highest frequency of monoclonal immunoglobulin components

1120/60 invariably had a low background immunoglobulin value at various examinations during the short medical history but a rapidly growing M-component (IgGL) which increased in concentration from 0 57 gram/100 ml to 1 41 gram/100 ml in 6 months. He also had free lambda-chains in the blood The lymph node and the bone marrow contained occasional plasma cells of normal appearance

1147/65 had at the first electrophoretic examination 2 27 gram/100 ml diffuse immunoglobulin without signs of activity Ten electrophoretic examinations in the course of the disease showed values between 1 74 and 3 15 gram/100 ml for immunoglobulins mostly without signs of activity Plasma cells were sparse in the lymph node but abundant in the bone marrow

855/67 had a long history with multiple organ symptoms interpreted as autoimmune disease (test for antinuclear factors positive) He had a diffuse increase of immunoglobulin already 9 years before the diagnosis 20 years before death. At the time of diagnosis the values were around 5 gram/100 ml. After splenectomy (because of lymphoma) the values fell roughly by 50 % but afterwards rose to reach a maximum level of 6 7 gram/100 ml. Treatment with chlorambucil was started and the values fell considerably For about 6 months the electrophoresis showed an IgM monoclonal component with a maximum concentration of 2 5 gram/100 ml. During corticosteroid therapy this component disappeared and during the last 5 years of his life the patient had diffuse hyper-immunoglobulinemia with values varying between 2 5 and 4 5 gram/100 ml Eight examinations of the bone marrow during the disease had shown massive plasmocytosis but no infiltration of the lymphoma. Lymphoma tissue in the lymph node showed occasional plasma cells. Necropsy revealed HL.

1107/69 had initially 1 73 gram/100 ml diffuse immunoglobulin which persisted at that level at 5 electrophoretic examinations, generally without signs of activity The lymph node contained occasional plasma cells as did the bone marrow

705/70 had at the time of diagnosis 1 78 gram/100 ml diffuse immunoglobulin. Two years after onset when he was being treated the immunoglobulin values were close to the lower limit of the normal range The urine then contained an M-component in the form of kappa-chains in low concentration The examination of the bone marrow at the time of diagnosis revealed 88 % atypical lymphoid cells and occasional plasma cells The lymph node showed abundant plasma cells.

2?0/72 had at the time of diagnosis 2 7 gram/100 ml oligoclonal immunoglobulin The increase persisted for about 2 years and afterwards the value became normal

The urine contained an increased amount of kappa-chains (amount not determined) The lymph node contained abundant plasma cells the bone marrow a normal number

In all the cases the plasma cells of the nodes and of the marrow were morphologically normal. "Lymphoplasmacytoid" cells with an intermediate morphology between lymphocytes and plasma cells were never seen

LLD-4 In this group there was no dominating pattern of immunoglobulin values. There was a general trend to falling values during the course of the disease but half of the patients examined late in the course still had normal or high values. One patient (397/59) had a small monoclonal fraction in $\beta 2$ which was not further classified or quantified

One case (451/61) had very high levels throughout Initially the diffuse immunoglobulins were 3 29 gram/100 ml. The value fell somewhat during treatment, but in all examinations performed the values were high and even just before death it was 2 42 gram/100 ml without any other signs of activity The lymph node contained numerous plasma cells (fig. 42) and a very occasional large blast cell similar to those seen in LLD-3 could be found. The picture thus was somewhat dubious as to classification but as almost no normal appearing lymphocytes were present it was assigned to LLD-4

LLN All of the patients examined early in the course had normal immunoglobulin levels. There was a general tendency to falling levels, especially after therapy but most of the patients examined retained a normal reactivity during infections One patient (272/73) constantly had background immunoglobulin around the lower limit of the normal range and an M-component (IgGL) of about 1 gram/100 ml. Judging from determinations made on several occasions this concentration was constant The lymph node contained only an occasional plasma cell. The bone marrow examination for lymphoma infiltrates at the time of the diagnosis was negative The specimen contained 4 % plasma cells, with occasional large nucleolated cells, but did not show a clear picture of myeloma.

Blood groups. As far as could be judged from the small figures, the distribution of AB0 and Rh-blood groups was normal for the population both within the groups and in the material as a whole This also holds for the total necropsy material.

VI Necropsy findings.

LLD-1 In 9 of the 13 cases the histologic findings at necropsy were of the same type as those seen in the biopsy specimen. Four had HL. The 9 patients with an unchanged picture had survived on the average 44 months. After the exclusion of the patients who had died from some intercurrent disease the mean survival time was 58 months. The corresponding figure for the patients with HL was 51 months including the case of myeloma excluding this case also 58

Generalised involvement of the lymph nodes was seen in all cases with unchanged histologic appearance of the infiltrate But the inguinal lymph nodes were of dubious value for making a diagnosis in 3 and the axillary nodes in 1 As for IF in the necropsy specimens see chapter 6 and chapter 8

The bone marrow showed lymphocytic infiltration in all 13 cases. In 11 it was dense and quite diffuse Two had focal infiltrates where the lymphocytes had for

med compact and frequently perfectly round foci while the parenchyma in between showed little or no lymphocytic infiltration In these 2 cases the WBC shortly before death were about 20 000 which were not the lowest found After treatment with cyclophosphamide 1 case (586/71) finally had severe leukopenia with about 50 % lymphocytes, but showed dense diffuse infiltration After cytostatic therapy one (1107/73) finally had a normal WBC but dense diffuse infiltration of the marrow

One (136/58) had also multiple myeloma diagnosed at the same time as CLL. The bone marrow showed characteristic foci, which consisted entirely of myeloma cells without lymphatic infiltration The surrounding parenchyma exhibited diffuse lymphocytic infiltration No extra-skeletal changes of myeloma were seen.

Two (1332/68 and 586/71) had no lesions in the liver or spleen. Both had been treated with large doses of cyclophosphamide. But the lymph nodes showed changes also in these 2 cases.

In the other 11 cases changes were seen in the liver and spleen The weights of the spleen varied between 150 gram and 1900 gram. The mean weight in the cases with infiltration was 770 gram The weight of the liver varied between 1340 and 2930 gram with a mean of 2030 gram The liver infiltrates had the character of an expansion of the portal tracts sharply outlined against the parenchyma.

In 11 cases the kidneys showed microscopic lesions They had the character of an infiltrate in the connective tissue around the vessels and especially in the cortical arteriosclerotic scars. The renal pelvis was represented in sections in 8 cases, all with lymphocytic infiltration of the fatty tissue The lungs showed infiltration in 9 cases. The infiltration was seen around bronchi and vessels or subpleurally mostly in the areas where there is normally lymphatic tissue and it was difficult to recognize the borderline between normal and abnormal No tumorous infiltration was seen in any of the cases

In one case the tonsils were enlarged and there was considerable infiltration of the testicles. One case showed heavy infiltration of the subendocardial connective tissue

Four cases had HL in at least one organ. One of them had microscopic HL-foci in the bone marrow the others showed only lymphatic infiltration without HL in the bone marrow Two had HL in the spleen and 3 in the liver while all had HL in some lymph node HL in LLD-1 is discussed in chapter 9

LLD-2 In both cases there was terminal leukemia One of the patients (671/66) survived 148 months and necropsy showed generalised infiltration of the lymph nodes spleen, liver and bone marrow with the same type of cells as in the biopsy specimen. The other (663/58) died 16 months after the diagnosis of leukemia. Necropsy showed diffuse myelofibrosis with infiltration of lymphatic cells (fig 14) Lymph nodes liver and spleen showed a peculiar lympho-histio-fibrocytic type of infiltration (figs 15 16) No extra-lymphatic tumours were seen in these two cases.

LLD-3 The necropsy findings are summarised in table 7 Four of the 7 cases had developed lethal HL. They had survived on the average 45 months The corresponding figure for the other 3 cases was 76 months but 2 died of non-lymphomatous diseases.

	Lymph nodes		Spleen	Liver	Bone marrow	
	All	5	6	7	Diffuse	4
	Exam. incomplete	2			Focal	2
					Normal	1
HL 4 cases		3	1	2		0
Remarks			One splenectomised because of lymphoma	Always portal tracts		

Table 7 Necropsy findings in LLD-3 (7 cases) The figures denote number of cases with affection of the organ in question by LLD-3 or HL.

1140/71 had preponderantly lymphocytic lymphoma in all the lymph node sites In the diffuse lymphatic infiltration there were foci of a bizarre-celled malignant tumour which was difficult to classify (figs 31 32) It resembled Hodgkin s disease It was not characteristic however and for the sake of simplicity it is included in the table as HL.

Examination of the peripheral blood had been performed within the last few days in all of the patients except one Five of them had a raised lymphocyte percentage with atypical cells The sixth patient (855/67) had a massive neutrophil leukocytosis. The necropsy specimens showed HL with necrotising arteritis (figs. 173-175)

In 2 of the patients the nodal examination was not complete One of them (1107/69) had lymphomatous nodes in the mediastinum. The other nodes were of normal size but were not examined microscopically The other patient with incomplete nodal examination had generally enlarged nodes.

The nodes engaged by HL were in all the cases in the mediastinal or retroperitoneal sites.

The bone marrow infiltration was generally not so dense as in LLD-1 In case 1140/71 with diffuse infiltration the pathological cells were rather sparsely distributed The foci in cases with focal infiltration were never well demarcated

The splenic infiltrates often had a slightly nodular appearance but no well demarcated follicle-like structures were ever seen Case 220/72 had large amounts of hyaline in the spleen

The lymphocytic infiltration of the liver was always confined to the portal tracts. The appearance was histologically identical to LLD-1 i.e., expansion of the portal tracts without infiltration of the parenchyma

No tumour formation was seen outside the lymphatic system in any of the patients in this group

LLD-4 The necropsy findings are summarised in table 8

	Lymph nodes		Spleen		Liver		Bone Marrow		Extra lymphatic tumours 7 cases	
	All	10	Diffuse	10	Portal tracts	10	Diffuse	7	Stomach	3
	Both sides of diaphragm but some nodes normal	2	Tumorous	1	Tumour	1	+ tumour	1	Skin	3
	Exam incomplete	1	Splenectomy	1	Normal	2	Focal	4	Adrenals	2
			Normal	1			No exam	1	Lungs	1
									Heart	1
									Pleura	1
									Pancreas	1
									Colon	1
									Appendix	1
									Ovary	1
									Dura	1
									Diaphragm	1
HL 1 case	1 (all)		HL case splenectomised			1		1	Soft tissues of pelvis	

Table 8 Necropsy findings in LLD-4 (13 cases) The figures denote number of cases with affection of the organ in question by LLD-4 or HL.

One of the patients (451/61) had developed HL This patient had survived for 27 months. He was leukemic during the entire course Including this one 8 of the patients had leukemic values at the time of death. Another 2 had atypical lymphocytes in a raised percentage and only 3 had normal numbers of WBC and lymphocytes.

Including the HL-patient 12 died of lymphomatous disease One died already after 5 months of myocardial infarction

In 5 of the cases some of the tissues examined showed a histological pattern of the lymphoma which could be suspected of nodularity though no really well demarcated nodules were ever seen.

In 10 cases liver infiltrates were confined to the portal tracts. When small, these infiltrates could hardly be differentiated histologically from those of LLD-1 or LLD-3 When large however there was a tendency of infiltration into the parenchyma which was not seen in the aforementioned groups, where the demarcation between portal tract and parenchyma was always sharp The case with the tumour in the liver also had some slight portal tract infiltration The group was characterised by a high percentage of cases with extra-lymphatic tumours, see table 8

Six of the cases had diffuse infiltration of the kidneys Five of them were leukemic at the time of death one had a raised percentage of atypical lymphocytes. The infiltration of the kidneys differed from that in the preceding groups in that they were generally situated deeper and were most dense at the corticomedullary junction. The tumour infiltration separated the glomeruli and tubuli by wide streaks of cells, similar to what is seen in blastic leukemia

Cytologic detail may be somewhat difficult to appreciate in necropsy specimens. In almost all the cases, however there was in places a seemingly more immature cytology than in the biopsy specimens This was not of HL-type but often resembled undifferentiated lymphoma However as a rule the histological type of LLD-4 was readily identified in most parts of the infiltration

LLN The necropsy findings are summarised in table 9

Lymph nodes		Spleen		Liver	Bone marrow		Extra-lymphatic tumours. 5 cases	
All LLN	1	Diffuse	2	See	Diffuse	1	Pleura	4
All LLD	1	Tumorous HL	2	text	Focal	1	Stomach	2
All HL	1	Normal	2		Nodules of HL	2	Lungs	2
HL in non-irradiated	3				Aplastic	1	Skin	2
					Normal	1	Adrenal	1
							Pancreas	1
							Dura	1

Table 9 Necropsy findings in LLN (6 cases)

Four of the 6 patients had widespread HL in the necropsy specimens. They had survived on the average 47 months (34-65) and they all died of lymphomatous disease The other 2 patients also died of lymphoma and survived for 5 and 70 months

All of the patients had had involvement of all the lymph node sites on some occasion In 3 no lymphoma was found in the peripheral nodes at necropsy but these sites had been irradiated

One of the patients had a tumorous HL in the liver one had some slight lymphoma infiltration in the connective tissue of a liver cirrhosis, 4 had no infiltration of the liver Two of the patients had tumours in the kidneys, 4 had no kidney infiltration

Four of the patients had extra lymphatic lesions which were HL one had extralymphatic lesions of LLD-4 type

Four of the patients had leukopenia just before death, 2 had normal values.

VII Natural history of some groups of lymphoma as judged from a retrospective analysis of cases examined on various occasions, and followed up for a long time.

The duration of the symptoms reported by the patients was remarkably uniform in all the groups. Most of them reported a swelling of the lymph nodes and/or a deterioration of the general condition for 6-12 months before the examination. But there were exceptions with a long subjective or objective previous history This holds especially for LLD 3

LLD-3 Two of the patients in this group survived only for 7 months (1120/60 and 1140/71)

1120/60 belonged to a family with polyposis of the colon. Because of this he was checked now and then but nothing pathological was found until 7 months before death, and then the enlarged nodes were diagnosed incidentally As he had a generalised disease and a raised lymphocyte percentage in the peripheral blood (WBC 6,200 lymphocytes 68 %) he must reasonably had had the disease for some time but it had been overlooked at the control examinations and he had felt quite fit. He was treated with radiotherapy and chlorambucil. One month before death very rapid deterioration with high fever and rapid enlargement of all nodes. Necropsy demonstrated HL.

In case 1140/71 enlarged nodes had been reported for "more than 1 year" She sought medical attendance 7 months before death because of a beginning deterioration of the general condition All the nodes then were enlarged and the bone marrow showed a very slight infiltration with pathologic cells. WBC 4 600 lymphocytes 42 % Treatment with irradiation and cytostatics was without effect and during the last 2 months of life the patient developed a severe anemia and trombocytopenia, and bouts of high fever She died of hyperpyrexia Necropsy revealed a bizarre-celled tumour most closely resembling Hodgkin s disease

Case 220/7? reported a feeling of a lump in the abdomen for about 1 year before she sought medical attendance She then had a huge splenomegaly and generalised lymphadenopathy and bone marrow infiltration. WBC 4 100 lymphocytes 6? %
This patient had for a long time been treated with diphenylhydantoin because of epi-

lepsy As it has been claimed that such therapy may be causative of lymphoma it may be mentioned that she was the only patient in this entire series treated with anti-convulsants. The patient now was treated with corticosteroids. Leukemic values appeared 20 months before death but she was in good condition until she died of an exacerbation of chronic pyelonephritis At necropsy still LLD-3

The other 4 patients had signs of a long lymphoma history

Case 1147/65 was interesting because the course of the disease had been studied for 127 months. The diagnosis was made incidentally when the patient sought advice because of myalgia of the neck. Some small cervical lymph nodes were noticed and a pea-sized node was removed for study and showed the picture of lymphoma. But no malignant diagnosis was made and the blood was not examined microscopically The patient was afterwards symptom-free for more than 3 years apart from very slowly growing cervical lymph nodes. She then returned because of gynecologic symptoms. The WBC was still normal but with 65 % lymphocytes. The cervical lymph nodes had grown to twice the size of a pea and similar nodes had appeared in the inguinal region. Re-biopsy (38 months after the first) showed more compact infiltration but the same cytologic picture The diagnosis of lymphoma was now regarded as firm and all peripheral sites were irradiated From time to time enlargement of lymph nodes appeared in different areas and was treated successfully The patient felt well About 5 years before death the spleen became palpable and from then on the patient 's general condition became slowly worse Two years before death a leukemic blood picture appeared with a maximal WBC of 35 000 with 90 % lymphocytes. The WBC fell again after irradiation of the abdomen, and the last 2 years she had a normal WBC with a high percentage of lymphocytes. About 3 months before death the lymph nodes grew rapidly and the patient became cachectic. Post mortem showed a more polymorphous picture than the node biopsies, but without diagnostic lesions of HL (corresponding to the picture of "polymorphous immunocytoma" see chapter 12)

Case 855/67 was one of the longest survivors in the entire series. He survived 137 months after the diagnosis. Already 5 years before the diagnosis there was periportal lymphocyte infiltration in a liver biopsy specimen obtained because of enlargement of the liver (specimen no longer available) These infiltrates need not however be ascribed to lymphoma For several years the patient had then had fluctuating enlargement of the lymph nodes in many sites If this enlargement of the lymph nodes was due to lymphoma the survival from the first appearance of symptoms would be almost 20 years, the first 10 without specific therapy But that patient had a remarkable clinical picture with chills and malabsorption as well as various positive serologic reactions and a massive diffuse increase of the immunoglobulins Necropsy revealed liver cirrhosis and necrotising arteritis as well as HL. Perhaps the case should be interpreted as chronic immunopathy with a hyperactive lymphatic system eventually developing into malignant proliferation resembling what has been described in other auto-immune conditions (see for example 48) At any rate the biopsy specimen of the lymph node 137 months before death showed lymphoma For a long time the percentage of lymphocytes was slightly increased with atypical cells

in the peripheral blood. The last 6 months the patient had deteriorated rapidly and died in a septicemia-like condition resistant to all treatment The liver and some nodes showed HL and the HL-tissue necrotising arteritis.

Case 1107/69 reported weakness with a marked tendency to infections during the last 2 years before the diagnosis. During this time the E S R. had for some unknown reason been raised After the diagnosis the patient survived 61 months during which his disease was dominated by a tendency to infections and fatigue but he had no local symptoms apart from enlargement of the mediastinal lymp nodes. The WBC fluctuated irregularly between normal and 14 000 with about 60 % lymphocytes No treatment was given He died from myocardial infarction The findings at necropsy showed the same histologic picture as the lymph node biopsy specimen.

Case 705/70 reported enlargement of the cervical lymph nodes for 5 years before the diagnosis, but his general condition had been unaffected He survived 27 months after the diagnosis One month before death leukemia appeared During the last 4 months of life he deteriorated rapidly and the mediastinal lymph nodes grew considerably at X-ray examinations. Necropsy showed HL in them while the other infiltrates had the picture of LLD-3

It thus appears that the patients in this group may have their lymphoma for a very long time without effects on the general health. Also the growth of the nodes may be very slow It appears probable that the patients may have their disease for a long time without seeking medical advice Both of the patients who survived for only 7 months died of HL It is not unreasonable to assume that they had had asymptomatic LLD-3 for a long time before that Two of the other patients who did not survive so long died of some disease other than lymphoma Much suggests that the natural history of this type of lymphoma is at least 10 years

Judging from the above findings, the course of the disease is roughly as follows.

After a probably long aleukemic pre-stage the percentage of lymphocytes in the peripheral blood gradually increases, in the beginning without having any notable effect on the WBC During this phase enlargement of the organs may be only mild and escape notice by the patient The bone marrow shows sparse infiltration This stage often lasts for several years (in 1107/69 the bone marrow examined at necropsy 5 years after diagnosis was still only sparsely affected) The WBC and the percentage of lymphocytes show a gradually increasing tendency but the values fluctuate spontaneously and vary between mildly leukemic and normal. The cells in the blood have the same appearance as in the tissue infiltrates with the exception that only a small percentage of the blast cells leave the tissue The percentage of immature cells is generally lower in the marrow than in the affected nodes The atypia of the cells in the blood is by no means always striking and can be readily missed by an inexperienced examiner Gradually the bone marrow infiltrate becomes denser and the cellular picture is dominated by tumour cells (1147/65 57 months ante mortem 705/70 at diagnosis, 7 months ante mortem) A critical level is reached when an increasing number of tumour cells are rather suddenly released into the blood This is not necessarily combined with a clear clinical deterioration but it is a sign that the disease is approaching its final phase The duration of the clearly leukemic phase was 23 months in 1147/65 and _0 months in ?20/7 705/70 died already 1 month after

the appearance of the leukemia, but in that case HL developed in the mediastinal lymphomas

The leukemic phase may thus last for more than 2 years. During this phase the clinical picture and the blood picture resembles CLL. In a fairly high percentage of the cases the disease changes its biologic character and HL supervenes. The patient then soon dies. HL probably always starts in the lymph nodes and is not often seen in the bone marrow Possibly the development of HL and the development of a leukemic blood picture are unrelated phenomena the first taking place in the lymph nodes the second being related to the state of the bone marrow

LLD-4 Most of the cases in this group reported symptoms for less than 12 months before diagnosis. Two patients (762/65 and 963/66) had signs of a long history however It is noteworthy that the lymph node biopsy specimens from these two cases were those with the smallest percentage of blast cells in LLD-4 In both of them the blasts had to be searched for carefully before found.

Case 762/65 sought medical advice because of gynecologic symptoms 126 months before death. Examination then revealed enlargement of an inguinal lymph node which microscopically proved to be lymphoma But the clinician doubted the diagnosis and no treatment was given The patient afterwards felt quite well for 5 years although the inguinal lymph nodes gradually grew in size. She was then operated upon because of ileus (adhesions) The abdominal lymph nodes appeared to be normal as did the liver and spleen She afterwards felt well apart from gradual enlargement of the inguinal nodes for more than 3 years, after which there was an accelerated enlargement of the nodes and the liver and spleen became enlarged. The blood picture was still normal but her general condition now deteriorated Biopsy of a lymph node (111 months after the first) showed the same cellular picture Radiotherapy of the peripheral sites was given and leukopenia developed which about half a year before death was followed by increasing WBC and about 3 months before death leukemic values appeared reaching a maximum of 194,000 with 94 % "lymphocytes" At necropsy the infiltrates were of unchanged histologic appearance The disease was thus diagnosed incidentally more than 10 years before death. For 8 years the patient had been symptomfree after which signs of dissemination and clinical disease appeared During the first 8 years the enlargement of the lymph nodes was so insignificant that the patient might very well have not noticed it

Case 963/66 was in an infirmary because of weakness due to old age Certain routine laboratory studies were made there Eight years before the diagnosis the WBC had been normal and the lymphocytes (55 %) slightly increased. Three years before the diagnosis he had slightly increased WBC 12 000 with 55 % lymphocytes, and mild trombocytopenia 90 000/μl. Four months before the diagnosis the WBC had been normal (no differential count) and at the time of the diagnosis the WBC was 71,000 with 89 % lymphocytes. The patient died 5 months after diagnosis of leukemia It is of course not possible to know with certainty whether these mild hematologic abnormalities had anything to do with his terminal lymphoma but in view of the history of case 762/65 reported above it does not appear unreasonable to assume that they had.

These two cases with very few blast cells in the nodes possibly represent a special form of LLD-4 with a more prolonged early course but the cases were too few to separate as a special group and the general appearance of the nodes was so similar that they were grouped together with other cases of LLD-4

The history of 451/61 is also given because this case had many similarities to LLD-3

The patient reported about 6 months disease before the diagnosis. He was then leukemic. Twelve months later a new lymph node was examined and showed the same picture. Fourteen months later he died and the lymph node site which was biopsied last showed exclusively HL, which thus must have developed within about a year The lymph node biopsy specimens were undoubtedly of type LLD-4 but the tissue contained a very occasional cell similar to the large immature ones of LLD-3 Also large amounts of morphologically normal plasma cells were seen The HL tissue in the necropsy specimens was very similar to that of cases of LLD-1 or LLD 3 see chapter 9 It may be that transitional forms between LLD-3 and LLD-4 exist

Several of the other cases of LLD-4 had been in hospital for other diseases for varying times before the diagnosis of lymphoma Nothing in the records indicated any abnormality of the lymphatic system or of the blood during these stays in hospital.

LLN Two of the patients had a long pre-clinical history (300/65 and 609/69) These two cases had the most pronounced nodularity and likewise the most prominent histiocytic component in the nodules of all patients in the series. Both patients died from HL.

300/65 survived 34 months after diagnosis, but reported growth of the circumference of the neck "for many years" The patient had a fluctuating, generally in creased percentage of atypical lymphocytes in the blood Already 14 months after diagnosis biopsy showed development into HL. A further 18 months later re-biopsy demonstrated diffuse HL. Twelve months later necropsy revealed generalised HL. The transition to HL thus presumably began about 2 years before death.

609/69 survived for 65 months after the diagnosis but had noticed an increase in the circumference of the neck for 4 years About 2 years before death atypical lymphocytosis began to appear but the values were never leukemic. Re-biopsy after 30 and 33 months showed an unchanged picture but after a further 30 months a tumour appeared in the gingiva It was pure HL. The patient became rapidly worse and within a month he died from generalised HL

Patients with LLD-1 who developed HL are discussed in chapter 9

Some case histories are summarised in fig II The 2 cases with very few blasts are presented at top in LLD-4 A rough estimation of the mean survival after first symptom or sign would be 80 months for LLD-3 and 55 months for LLD-4 (the two cases with very few blasts 120 months, the others 45 months) and for LLN 50 months.

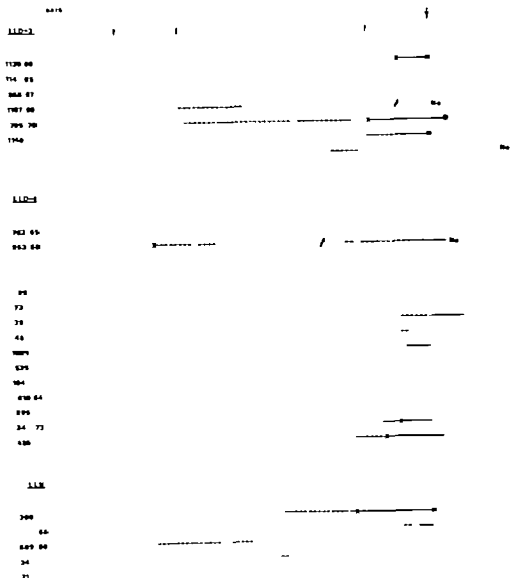


Fig. II. Summary of case histories in LLD-3 LLD-4 and LLN

Line represents course from diagnosis to death. Non-leukemic phase to the left of the vertical line continuous leukemic phase to the right of this line Prediagnostic phase with symptoms or signs probably due to lymphoma.

x First recording of more than 45 % lymphocytes in differential count.

/ First recording of WBC more than 10 000 with more than 45 % lymphocytes

• HL in necropsy specimens.

No Death due to some disease other than lymphoma.

VIII Discussion of biopsy specimens of the lymph nodes.

The smallness of the groups makes it difficult to evaluate the relevance of the classification, as no statistical differences were found owing to the wide variation of the observations. Larger series of malignant diseases of the lymph nodes have been published. The present material is presented primarily to permit comparison of the aleukemic lymphoma groups with the CLL material. It is of course a limitation that the material consisted only of patients who had died because it may result in an erroneous impression of the effect of recent developments in treatment During a major part of the investigation period treatment with modern drastic radiotherapeutic and cytostatic methods was not in use and therefore the series may perhaps give a more correct picture of the natural history of the diseases. The survival rates do not, of course hold for the situation to-day

The range of variation of individual variables must be wide in any series where the diseases were diagnosed at different intervals after their true onset It might therefore be difficult to demonstrate numerically significant differences even between apparently different processes. In the present investigation attemps were made to reconstruct the course from the onset of symptoms but laboratory tests during the preclinical and policlinical phases were sporadic for which reason interpolation was often necessary The groups are too small for meaningful statistical comparison of survival dates and laboratory values.

Many investigations have shown the clinical significance of Rappaport s "differentiation" of the lymphocytic lymphomas, at least regarding survival. The differentiation concept was not used here because of a desire to replace the term by two others describing different variables. Moreover I also found it difficult to place in Rappaport s system the tumours, which I called LLD-3 and small-cell cases of LLD-4 Rather than introducing a term such as intermediate differentiation I decided to use the more neutral numerical designations described

LLD-1 appeared to be the characteristic picture of the lymph nodes in CLL. All the patients were leukemic and all examined had bone marrow infiltration at the time of diagnosis. General enlargement of the palpable nodes was the rule. Exceptions were seen but it is well known among pathologists that infiltration might exist in normal or almost normal-sized nodes in CLL and also that the liver and spleen need not be markedly enlarged in spite of infiltration This lymph node picture probably always represents a systemic disease involving practically all lymphatic tissues from the very beginning If an initial aleukemic stage exists, it is often not possible to diagnose it histologically because typical lesions are seldom seen in untreated aleukemic patients at necropsy or in surgical specimens

LLD-2 may appear to be very different on superficial examination Few mature lymphocytes were seen while such cells dominated the picture of LLD-1 On the other hand all the cellular components of LLD-2 were also found in the IF of LLD 1 Cases of LLD-1 with very large IF sometimes had portions with confluent IF and thus a picture with transitions to LLD-2 Such nodes should according to Rappaport be classified as partly well partly poorly differentiated Still the patient may have ordinary CLL from a hematologic point of view

The two cases of LLD-2 differed from one another clinically but both were generalised initially One was leukemic the other non-leukemic. As in LLD-1 two generations of cells were readily recognized in the bone marrow The ratio between mature and immature cells was the reverse LLD-2 presumably corresponds to the condition which Galton et al. called prolymphocytic leukemia, a term also used for other conditions (19) These authors described under the name prolymphocytic leukemia, a rare form of lymphatic leukemia in adults. They felt that one should distinguish this disease from chronic and acute lymphatic leukemia and from chronic and acute lymphosarcoma cell leukemia. No biopsies of the lymph nodes were obtained in their cases and the description of the findings at necropsy was incomplete. The cases were characterised by less prominent enlargement of the lymph nodes but marked hepatosplenomegaly and very high lymphocyte values in the blood The morphologic appearance of the blood and bone marrow is described in a way corresponding to my cases of LLD-2 Galton et al. felt that the disease had a poor prognosis but they found signs of a possible long inapparent stage before the condition was diagnosed. LLD-2 thus seems to be the tissue manifestation of prolymphocytic leukemia In Rappaport s classification, LLD-2 must be assigned to the poorly differentiated, diffuse lymphocytic lymphoma group

LLD 3 was the most polymorphous group Histologically it had some similarities to both LLD-1 and LLD-4 On superficial examination it is easy to confuse the pic ture with LLD-1 because of the predominance of small lymphocytic cells IF are not present however and on careful scrutiny it was apparent even in histological sections that the lymphocytes had a greater variability than in LLD-1 and that many atypical forms were present This trait was better appreciated cytologically in smears. Immature cells similar to those of LLD-1 and LLD-2 were present but often the general polymorphism and atypia with nucleolated forms of lymphocytes obscured the difference between the immature and mature components in smears and the generations were not so easily appreciated as in LLD-1 Clinically the cases appeared to be very dissimilar with a great range in the variation of survival and "acuteness" As has been argued however it does not appear unreasonable to assume that the patients with a short survival had had the disease for a long time before it was diagnosed. Many cases had an extremely long survival with very few symptoms and signs and it appears probable that this kind of lymphoma has the best prognosis of those dealt with here

From a hematologic point of view the most characteristic findings for a great part of the course appeared to be slight bone marrow infiltration and a blood picture with normal or slightly raised WBC and a raised lymphocyte percentage and the oc curence in the blood of atypical lymphocytes but a preponderance of normal or almost normal forms. The large immature cells of the lymphatic tissue were found only in very low numbers in the bone marrow and hardly at all in the blood. It appears probable that every case will sooner or later have a raised lymphocyte percentage. Only in one case was the percentage not raised This case (1140/71) however had lymphocytes close to the upper limit of the normal range at diagnosis and then sur vived for only 7 months and was treated intenselv with cytostatics and irradiation. More than half of the cases had leukemic values at some time and in this phase the

disease closely resembled CLL, but the lymph node picture did not become that of LLD-1 and to a trained observer the blood and bone marrow pictures were different. The leukemic phase may last for several years

The great majority of cases appeared as a systemic disease from the beginning, but exceptions were seen without general enlargement of nodes or bone marrow infiltration. As to the last however it may be difficult to exclude it as it may be very slight and often focal Smears alone are not enough for the examination, but probably occasional small foci can be missed also in sections. This may apply also to necropsy specimens unless many sections are examined. In one of the cases no bone marrow infiltration was ever diagnosed, but atypical cells appeared in the blood now and then so it appears improbable that the marrow was spared But in spite of the long survival of the patient the bone marrow infiltration if any must have been very slight In no case was it proved at necropsy that unaffected nodes were present but in one microscopically incompletely examined case there were normal-sized nodes in some sites so it may be that the process remains confined to a single lymph node group in occasional cases However this case also had bone marrow infiltration. Liver and spleen became engaged in all cases sooner or later

A large percentage of the cases developed HL terminally This is probably the reason why so few cases with this lymph node picture are seen in necropsy specimens (see chapter 6) Many patients probably live with LLD-3 for a considerable time before they seek medical advice or die without a clinical diagnosis when HL appears The picture of HL may be found in some organs but LLD-3 in the bone marrow (see chapter 6) which argues in favour of this view

The immunoglobulin values require comments All the cases of LLD-3 examined early in the course had high diffuse immunoglobulin levels. A varying amount of apparently normal plasma cells were found in the nodes in all cases. This contrasts with what is the rule in LLD-1 However the plasma cells also occurred in the bone marrow and without evident correlation with the existence or the degree of lymphoma infiltration. Because of this and in view of the polyclonal increase it does not appear probable that the plasma cells are an integral part of the tumour proliferation, but a concomitant phenomenon possibly due to a reaction to the tumour as most cases had an increased value of immunoglobulins also without other inflammatory signs in the electrophoretic pattern. Many cases also had a monoclonal component however which was possibly a product of the tumour cells.

In contrast to the above mentioned groups, LLD-4 often appeared to have a localised stage initially Roughly half of the patients had only one site or organ affected at the time of diagnosis and even at necropsy the dissemination was sometimes not complete But in the majority of cases the bone marrow was sooner or later involved diffusely or focally In most cases also atypical cells were released to the blood but initially the blood picture was most often normal A high percentage had leukemic values, but generally only for the last few months before death. Yet 2 cases were leukemic during the entire clinical course of about 2 years. Thus from a hematologic point of view the course is rather variable Also the immunoglobulin pattern was less consistent than in LLD-1 or LLD-3 and high normal or low values were seen but in the late phases low γ were most common, possibly due partly to treatment

Monoclonal immunoglobulin components may be seen but not so often as in LLD-3

The few nodular lymphocytic lymphomas appeared to be localised in a higher percentage than any of the diffuse groups. Also the blood picture was generally normal at diagnosis Atypical cells appeared in the blood in some cases, however but clearly leukemic values were not seen. But leukemia may be seen judging from the literature (64) and also from personal experience with similar cases not included in this study The frequency is generally given as about 25 % of all cases of nodular lymphomas (64) But LLD-4 sooner or later developed leukemia in about 60 % in this series. The bone marrow was often involved at necropsy in LLN but it was often a question of HL changes The development of HL was more common in this group than in LLD-4 which did not seem remarkable as the content of "histiocytic cells in LLN generally was higher than in LLD-4 But the picture of LLD-4 was sometimes seen mixed with that of LLN both in biopsy and necropsy specimens, so it appears certain that they are diffuse and nodular variants of the same process A high percentage of extra-lymphatic tumours were seen in both groups in contrast to LLD-1 LLD-2 and LLD-3 The immunoglobulin values of LLN were generally normal in the early stages, but monoclonal immunoglobulin components may be found also in this group They generally seem to be of type IgG (49)

Summarising the lymphocytic diseases in question could be separated in two groups LLD-1 and 2 which from the very beginning appear as systemic diseases, and LLD-4 and LLN which probably in the majority of cases have a localised stage LLD-3 appears to have an intermediate position Most cases are probably systemic from the beginning but the degree of bone marrow infiltration is often slight In occasional cases, the bone marrow is spared and also some lymph node groups may not be involved LLD-1 and 2 could be called the lymphocytic leukemias proper and LLD-4 and LLN the lymphocytic malignant lymphomas proper but LLD-3 is not easily classified as either leukemia or lymphoma and this separation appears to be of little use as the lymphomas may be leukemic and the leukemias (at least LLD-2) may be non-leukemic In Rappaport s classification LLD-1 would correspond to well differentiated diffuse lymphocytic malignant lymphoma. Possibly also LLD-3 and small-celled cases of LLD-4 with few blast cells would be assigned to the well differentiated group LLD-2 and the rest of the cases of LLD-4 would be classified as poorly differentiated All the nodular cases in this series would be classified as poorly differentiated

Occasional cases appeared to have traits of both LLD-3 and LLD-4 and the border between the two groups is possibly not quite sharp

LLD-1 is the morphologic manifestation of CLL and can generally be distinguished from leukemic lymphoma of other types. This conception argues against the conventional opinion that CLL is indistinguishable from well differentiated aleukemic lymphocytic lymphoma LLD-1 in the aleukemic form must be rare. There may be cases with morphological features intermediate between LLD-1 and LLD-3 (see later) but a case with an initial picture characteristic of one group does not develop a picture characteristic of the other LLD-3 may have a long leukemic course which is clinically difficult to distinguish from CLL. One might of course call this a variant of CLL, but the diseases appear to be different if one has a possibility

to follow them throughout their course

LLD-2 is a small group more closely related to LLD-1 than to other groups of "poorly differentiated lymphoma"

The nodular lymphomas have a tendency to progress towards diffuse growth. Whether this is a prognostically bad sign is not possible to decide from this small material. The lymphoma group also has a tendency to develop into HL. This may be seen more often with the nodular variants LLD-1 and LLD-3 often assume a more immature cytologic picture though not that of the lymphoma group proper but that of HL or Hodgkin s disease (see chapter 9) It is probable that LLD-1 can also undergo transformation to LLD-2 (see chapter 6)

As to the leukemic manifestations of the lymphoma group proper it appears probable that it is a consequence of heavy bone marrow infiltration However atypical cells may be seen in the blood with only slight and focal bone marrow infiltration and this also applies to LLD-3 The bone marrow picture in the leukemic phase of the lymphoma group proper may be quite immature. One might discuss the possibility that the patients had developed a new disease a leukemia unrelated to lymphoma e.g. caused by treatment Such a possibility is remote because preterminal leukemia is relatively common in this category while other cases of malignant diseases treated with similar methods rarely develop leukemia There may be some cases in this lymphoma group that develop the picture of undifferentiated lymphoma.

Chapter 5

A STUDY OF BONE MARROW SMEARS INTERPRETED AS LYMPHOCYTIC LYMPHOMA AND LYMPHATIC LEUKEMIA

Technically acceptable smears were available in 79 cases. (The case with CLL + myeloma was excluded from this part because of the special bone marrow picture) Histologic examination of the bone marrow and special examinations such as PAS-staining and enzyme cytochemical studies were performed only during the last years and will not be dwelt on here The classification is thus based on routine smears stained with the May-Grünwald-Giemsa stain

The bone marrow and blood smears were examined without knowledge of the final diagnosis. It proved extremely difficult to distinguish the pictures of LLD-3 LLD-4 and LLN Further this material contained some cases in which necropsy or lymph node biopsy specimens exhibited a picture of undifferentiated lymphoma but where the bone marrow picture was clearly lymphocytic and easily confused with that of LLD-3 or LLD-4 It appears doubtful whether it is meaningful to try to differentiate between these groups by the picture of the bone marrow The cytologic picture gave no reason to suspect nodular growth. The findings in the "non-leukemia group" will be discussed later but the cases were pooled in one group

It was suspected that a case might be of type LLD-2 if the smear contained lymphocytic cells, more than 50 % of which were clearly nucleolated and if their appearance corresponded to that of prolymphocytes as described for group LLD-2 above The bone marrow smears were accordingly divided into 6 groups.

1	corresponding to LLD-1 (see chapter 4)	42 cases
2	corresponding to LLD-2 (see above)	10 "
3	cases judged as lymphocytic malignant lymphoma of non-leukemia type (see above)	17 "
4	corresponding to the classical description of Waldenström s macroglobulinemia (see chapter 1)	5 "
5	unclassifiable in this scheme	1 "
1 3	doubtful whether group 1 or group 3	4 "

GROUP 1

This group consisted of bone marrow smears from 42 patients. 27 of the patients were men, 15 were women The average age at the time of death was 75 years for the men and 77 for the women. The clinical diagnosis was CLL in 42 cases.

Of the men, 18 died from their basic disease or some complication of it Four had HL and 1 Hodgkin s disease at necropsy The average survival time after the diagnosis of these 18 men was 53 months.

Of the women 9 died from their basic disease and a further 2 from miliary

tuberculosis. These 2 had well controlled leukemia and the tuberculosis should perhaps be regarded as a complication of the treatment Of the 9 three had HL at necropsy The average survival time of these 9 women was 66 months. The average survival time of the men + women who died from the disease was 57 months, thus practically the same figure as for LLD-1 in the lymph node material.

Of all 42 patients, necropsy demonstrated HL in 7 and Hodgkin s disease in one. The average survival time of these 8 was 67 months (30 180)

One patient (31/67) who died from Hodgkin s disease reported that a twin brother and a maternal aunt had died from leukemia but these cases could not be traced to control the correctness of the information given There was no known blood relationship between any patients in the series

The WBC at the time of diagnosis ranged between 10 900 with 70 % lymphocytes and 453,000 Some data are summarised in table 10

AT DIAGNOSIS

WBC x $10^3/\mu l$ 42 CASES

<100	50 %
100-200	25 %
>200	25 %
10-20	15 %

HEMOGLOBIN CONCENTRATION BELOW NORMAL LIMIT	25/40
THROMBOCYTOPENIA	15/30
COOMBS TEST POSITIVE	7/28
GENERAL ENLARGEMENT OF PERIPHERAL NODES	24/42
NO PALPABLE NODES	10/42
SPLEEN PALPABLE	18/42
LIVER PALPABLE	14/42
NO PALPABLE ENLARGEMENT OF ANY ORGAN	10/42

MAXIMAL VALUE OF WBC DURING COURSE x 10^3

≤50	23 8 %
51-100	23 8 %
101 150	9 5 %
151 200	9 5 %
201 500	26 3 %
>500	7 1 %

MAXIMAL VALUE IN SERIES: 1238 x 10^3

SIGNIFICANT HEMOLYTIC ANEMIA ON SOME OCCASION 4/42

Table 10 Group 1 of bone marrow series

The immunoglobulin values are included in table 14 Seven patients had on some occasion had small M-components 4 had an IgM-component in the plasma The light chain was determined in 2 1 kappa and 1 lambda. The component was not quantified in 1 case in the other 3 it had values between 0 23 and 0.30 gram/100 ml. One case had an M-component in a concentration of 0.30 gram/100 ml in β 2 it was not typed further Two cases had Ig μ L in the urine (amount not measured) Thus all these components were probably of an IgM-type. The 2 M-components in group 1 3 were both IgGK.

The 7 patients with M-components survived on the average 67 months, thus if anything longer than the group as a whole Two of the HL-cases and the case of Hodgkin's disease had M-components thus about 1 out of every 3 in the group and about 1 out of every 9 of those that did not develop HL or Hodgkin s disease The average age of the patients with M-components at the time of death was 68 years, thus below average arguing against the M-components being incidental to old age A further discussion of the relation of monoclonal immunoglobulin components and HL is given in chapter 9

Two patients had high diffuse immunoglobulin values late in the disease They had high values also early and both had shown signs of high activity in the electrophoretic patterns Two others had terminally extremely low immunoglobulin values, 0 12 and 0 06 gram/100 ml.

Cytologically there were 10 cases of large-cell, mature type in the bone marrow and 32 with small-cell, mature type Of the HL-cases, 2 belonged to the large-cell group 5 to the small-cell group In the case of Hodgkin s disease the cells were small.

One patient (immature +) had crystalline inclusions in the cytoplasm (low immunoglobulin level without M-component) Seven had immature cells ++ in the bone marrow and of these 5 also in the blood ++ while 2 had + Blood smears were available in a further 21 cases. They had immature cells + Of the 7 cases with ++ in the marrow 2 developed HL, while 5 HL-cases and the case with Hodgkin s disease had bone marrow with immature + HL was thus somewhat more common in the ++ group than in the + group but the figures were too small to show any significance

Intensely basophilic cytoplasm was found in 10 cases. Except for this the cells were not of plasmacytoid appearance but in those cases the cytologic picture was generally more polymorphous than in others in the group though still evidently different from group 3 Two of them developed HL. Three of the 7 cases with M components were included among these 10 (M-components were thus roughly 3 times as common among these cases as in the rest of the group)

There were thus no characteristics of bone marrow or blood picture to make it possible to predict with certainty whether the patient would develop HL or Hodgkin s disease

NECROPSY FINDINGS Apart from the 8 cases with HL or Hodgkin s disease the findings in the remaining 34 cases were of the type described earlier as LLD-I Generalised involvement of the lymph nodes was seen in 26 cases. One case was without diagnostic changes, the other 7 had 1 or 2 lymph node sites without dis

gnostic changes, always either inguinal or axillary The liver showed infiltration in 30 of 34 cases. The largest liver weighed 4 050 g. Microscopically the spleen had infiltrates in 30 of 34 cases Four of the spleens involved were of normal size (weight < 200 g) only 2 weighed more than 1 000 g (max. 3 100 g) Twenty-four thus weighed between 200 and 1 000 g. The bone marrow was diffusely involved in 24 cases focally in 6 One case was aplastic 1 was not examined. Two had no diagnostic bone marrow infiltration at necropsy They were hematologically normalised by therapy before death

Some cases showed tumorous lesions outside the lymph nodes. In one case the spleen contained a tumour-like grey white nodule the size of a walnut WBC terminally 90,000 In another case the liver showed multiple pea-sized grey-white nodules WBC terminally 225 000

Two cases had tumour like lesions outside the lymphatic system One of them (352/73) had several fist-sized soft tissue infiltrates in the retroperitoneum and in the renal adipose capsule They were grey-brown and very soft WBC terminally 370 000 One case (614/67) had a tumour like white infiltrate about 1 cm thick under the pleura and dura WBC terminally 216 000 In these cases the infiltrates consisted of the same type of lymphocytes as other infiltrates, and thus showed no direct signs of sarcomatous transformation No IF were seen. Such extra-lymphatic lymphocytic tumours without signs of HL appeared to be rare and probably occurred late in patients with a high WBC

The patient with the tumour in the spleen had also heavy diffuse infiltration in the corpus and cervix uteri which had produced a large palpable pelvic mass and profuse bleedings. The changes had clinically been interpreted as probably cervical carcinoma Otherwise this group contained no cases with notable organ enlargement (except the liver spleen and lymph nodes) because of lymphocyte infiltration

As for HL-changes, see chapter 9

Broadly speaking the findings in this group confirm those in the smaller LLD-1 material of node biopsies When the disease with this cytologic picture reaches clinical significance it is probably practically always leukemic The terminal development of HL was common also in cases with this cytologic bone marrow picture

GROUP 2

Of the 10 cases only 663/58 had immature +++ in the peripheral blood 671/66 had no lymphocytosis at the time of diagnosis but finally became leukemic however no blood smears were available from that phase Of the others 4 had immature ++ in the peripheral blood while 4 had immature + The blood picture in these 4 was of ordinary type for a mature CLL (figs 18 19)

It thus appears as if the bone marrow picture of type ? may be associated with the blood picture of type 1 This must be regarded as arguing for the assumption that both are variants of the same process Are there then any deviating features common to cases with a high percentage of immature cells in the bone marrow? The 10 cases in group are treated here together regardless of the blood picture. See also chapter 8 on immature cells

Six were men and 4 were women The average age at the time of death was 74

years (53 92) Two had died from non-lymphoma disease The average survival time for the remaining 8 was 48 months, thus somewhat shorter than in group 1 but the variation was wide (2 148) The WBC at the time of the diagnosis was normal in 1 case (4 200 with 37 % lymphocytes) The other cases had leukemic values ranging between 15,300 and 500 000 Only 2 of the patients had more than 100 000 at the time of diagnosis. In nearly all however the WBC reached a very high level some time during the period of illness. Six had on some occasion more than 150 000 4 more than 200 000 In one there was only 1 initial value 15,300 after which the patient survived a further 12 months but the course of the WBC is not known. 671/66 became leukemic about 8 months before death, and the WBC rose to at most 54 000

Six had hemoglobin values below the lower border of the normal range at the time of diagnosis. Two had abnormally high values 16 3 and 20 4 gram/100 ml. The patient with 20 4 gram/100 ml had had polycythemia vera for 7 years by the time the leukemia appeared and had repeatedly been treated with P^{32} Coombs test was performed in 6 cases and proved positive in 3 Significant hemolytic anemia was found on some occasion in 4 cases. Thrombocytopenia was noted at the diagnosis in 2 cases.

The immunoglobulin values are given in table 14 One M-component was found in the group (IgM)

Five of the patients had at the time of diagnosis severe splenomegaly 1 had moderate splenomegaly In 4 the spleen was not palpable Four had severe generalised enlargement of the lymph nodes in the others the enlargement was slight.

NECROPSY FINDINGS In 8 all the lymph nodes were involved 2 had no diagnostic changes. The liver and spleen were involved in all. The average weight of the spleen was 770 g (1 excluded because the spleen was scarred after infarction) The average liver weight was 1 740 g. The figures are not significantly above those in group 1 The bone marrow showed diffuse lymphocytic infiltration in 7 The remaining 3 (1320/64 655/63 and 663/58) showed myelofibrosis with diffuse lymphocytic infiltration. The lymph nodes in these 3 also showed fibrosing features as well as infiltration of histiocytes without malignant morphologic traits. 655/63 had stratified fibrous nodules in the lymph nodes with a zone of polymorphous HL-like tissue in the periphery One lymph node showed a focus of clear-cut HL (see chapter 9)

663/68 had in the beginning of the disease a slightly increased hemoglobin value and had for some time had an unexplained mild increase of the WBC with a normal differential count. 1226/65 had for a long time had polycythemia vera Another case had pernicious anemia.

In no respect did the group show any significant clinical differences from the mature CLL-cases assigned to group 1

The most remarkable are the 3 cases with myelofibrosis and fibrohistiocytic lesions in the lymph nodes. One might wonder whether this was due to a tendency to cellular death that was so marked as to result in fibrosis. An interesting finding was that one of the patients (not fibrosing) had polycythemia vera before the onset of leukemia and another (fibrosing) had possibly had mild myeloproliferation as judged

from the somewhat high values for hemoglobin and WBC One might consider the possibility of some relationship with the myeloproliferative group of diseases in these cases It might be of interest to note that mitogen stimulated lymphocytes have been found to produce colony-stimulating factor in vitro (53)

The findings were interpreted as indicating that groups 1 and 2 were different types of the same disease According to what is said later (see chapter 8) the mature lymphocytes are probably derived from the immature cells. It is then not unreasonable to assume that the cytology of the tissues is more immature than the blood picture In those cases where a higher percentage of immature cells are released into the blood the hematologic picture will be that of prolymphocytic leukemia. It is not possible to decide from these findings whether the picture of LLD 2 in the lymph nodes can occur also in such cases where the blood cytology is mature However in the light of the aleukemic case it appears probable This type of lymphatic leukemia thus appears to occur in an aleukemic form possibly because the immature cells in the tissue have a stronger tendency to adhere to one another than mature lymphocytes.

GROUP I 3

Four cases were referred to this group

109/67 was a woman who had died at 83 years of age after a course of 133 months. At diagnosis she had enlargement of the cervical lymph nodes, but the liver and spleen were not palpable WBC 124 000 with 95 % lymphocytes. Hb 12 0 gram/100 ml platelet count normal. Immunoglobulin values low Coombs test positive No signs of hemolysis Treated with corticosteroids and did well for several years. Differential count showed successive increase in percentage of "blasts which reached a maximum of 20 % Immunoglobulin values increased successively to abnormally high values and reached 1 8 gram/100 ml at which level they persisted for a year or so and afterwards fell shortly before the patient died WBC varied markedly with a maximum of about 250 000 The patient died after operation for carcinoma of the colon. Necropsy showed sparse diffuse lymphocyte infiltrates without enlargement of any organs. The bone marrow picture was of small-cell type with many irregular nuclei and many "diplococcoid" nuclei resembling the picture in 799/73 in group 3 with irregular chromatin structure but few with distinct nucleoli (fig 82)

Clinically the case resembled most CLL, but with an increasing percentage of atypical and immature cells in the blood

437/67 The patient was 63 years old at death Two hundred and forty-six months before death he had fallen ill with abdominal pain for which no explanation was found and which soon disappeared At that time he had 29 000 WBC with 78 % lymphocytes. Mildly enlarged tonsils otherwise no enlargement of any organ Hb 16 0 gram/100 ml E.S R 1 mm/ 1 hr The patient felt well for almost 20 years and belittled his disease but was followed up every fourth year and the WBC increased successively to reach a maximum of 174 000 Hb platelets and E.S R remained normal Five years before death the patient was examined for the first time with electrophoresis which showed a low immunoglobulin value 0 39 gram/100 ml and an M-component of type IgGK of 0 30 gram/100 ml Five later electrophoretic examinations the last just before death showed similar values Bone marrow exa-

mmation 4 years before death showed dense infiltration with cells of varying size and many with irregular nuclei and chromatin structure but few with distinct nucleoli (fig. 73) Many cells with deep nuclear clefts. The blood picture was similar (fig. 72)

Seven months before death a tumour developed in the mesopharynx which at biopsy was found to be HL (figs. 74 75) Radiotherapy was without effect and the patient died from extension of the tumour into the brain. WBC terminally fell during radiotherapy and corticosteroid therapy Necropsy showed generalised HL. The spleen contained IF The patient had thus had almost asymptomatic leukemia for 20 years and later developed HL from which he died within 7 months. The condition resembled most CLL.

1029/71 was a woman 63 years old at death, who after a traffic accident was found to have splenomegaly with no palpable lymph nodes. WBC 9,300 with 84 % lymphocytes. Hb and platelets somewhat low Immunoglobulins normal. Bone marrow aspirate showed fairly dense infiltrates of a type resembling that in group 3 with small cells with an irregular nucleus and chromatin structure and immature ++ But the blood contained mainly normal forms.

The patient felt well and did not seek advice for the following 6 years. She afterwards returned with gastrointestinal bleeding. WBC was then 66 000 with 90 % lymphocytes. The spleen had grown considerably while the lymph nodes were still of normal size Moderate thrombocytopenia The source of bleeding was not found Irradiation of the spleen was followed by severe leukopenia and thrombocytopenia and one month later the patient died from diffuse bleeding from the gastric mucosa.

During her last spell in hospital examination of a new bone marrow aspirate revealed atypical cells but in a low percentage relative to that of apparently normal lymphocytes. The blood picture showed only occasional atypical cells. The WBC on that occasion was about 70 000

Necropsy showed insignificant lymph node changes and focal bone marrow infiltrates as well as insignificant infiltration in the liver The spleen weighed 2,300 g but this was due to a thrombus in the portal vein, and it contained no residual infiltrate

Clinically and anatomically this case would best fit in with LLD-3 with the changes localised mainly to the spleen, but especially on the last occasion, the cytologic picture of the bone marrow was so mature and so little atypical that the case was assigned to the uncertain group The blood picture was throughout mainly of type 1 and it is at any rate uncertain to classify a case simply on the basis of the blood picture which can be dominated by morphologically almost normal forms also in bone marrow of morphologic type 3

913/72 was a man who died at 81 years after having fallen ill with pneumonia 49 months earlier No palpable enlargement of any organs WBC 15 800 with 72 % lymphocytes Mild anemia.

Immunoglobulin levels were high with a small M-component IgG 0.39 gram/100 ml The bone marrow showed 90 % lymphocytes with roughly equal distribution between lymphocytes of normal appearance and cells with uneven nuclei with small

nucleoli and irregular chromatin structure (fig. 81) The patient was in a good condition, but since the WBC showed a tendency to increase he was treated with corticosteroids after which the WBC fell to its original level. The immunoglobulin values fell but not to subnormal level The concentration of the M-component rose somewhat The patient died from myocardial infarction Necropsy showed insignificant organ lesions but small IF in some of the lymph nodes. The case resembled most CLL.

GROUP 4

The picture of the bone marrow was characteristic of Waldenström s macroglobulinemia in 5 cases (225/61 204/69 891/69 820/70 and V 251/73) Such a diagnosis required a finding of mainly small-cell lymphocytic type with preponderance of lymphocytes with a mature nucleus. The characteristics of the cytoplasm were regarded as not being essential. Neither were such "lymphoid reticulum cells" with almost total lack of demonstrable cytoplasm as described by e.g. Rohr (59) though they were often seen Further the diagnosis required a distinct plasma cell component and transitional cells between the lymphocytic and plasmocytic population and further an increase in the mast cells. The numerical increase in the mast cells is difficult to estimate because they tend to be destroyed in association with the preparation of the smear but in all the cases in this group the mast cells were so numerous that they were obviously increased An increase in mast cells was common also in group 3 and did not appear to be of any differential diagnostic value Another characteristic, which was not seen in all cases, probably due to the less satisfactory technical quality of the negative smears, was groups of cells made up of reticulum cells, lymphocytes, plasma cells and often mast cells (figs. 83 84). One cannot make a diagnosis simply on the basis of such groups because they occur also in other conditions, e g. often in LLD-3 Often but not always the plasma cells and lymphocytes exhibited intranuclear vacuoles (fig 85) and sometimes markedly angular plasma cells were seen (fig. 83) It would appear that such cells had become detached when being smeared on the slides and had dried in this shape before they had had time to become round In the tissue these cells have a tendency to be angular which is the most space-saving shape with maximal surface contact Cells with such a distinctly angular cytoplasm were seen in 3 cases, all with distinct groups of the type described In the other cases the smears were poor in cells.

Monocytes and blast-like cells of somewhat dubious classification were also often increased as was stainable iron Monocytosis was often seen in the peripheral blood In 1 case monocytes repeatedly constituted 15 to 20 % of the cells in the blood

In all 5 cases the clinical diagnosis was Waldenström s macroglobulinemia This also was the case in a further 2 patients in the Malmö-series In one of them the bone marrow had not been examined In one (99/62) the bone marrow picture was of another type which assigned it to the unclassifiable group All these cases are discussed together in chapter 7

None of the cases with a clinical diagnosis of macroglobulinemia had a bone marrow picture of the type seen in group 3 but LLD 3 and macroglobulinemia had certain similarities in smears, particularly the tendency to grouping of cells and increase in the number of mast cells

GROUP 5

99/62. This case had a cytological picture with some similarities to myeloma Clinically the case was macroglobulinemia and is described in chapter 7

GROUP 3

The diagnoses based on biopsy or necropsy specimens were as follows

LLD-3	7 cases
LLD-4	5 cases
LLN	2 cases
undifferentiated lymphoma	3 cases.

Twelve of these cases have been dealt with in chapter 4

Case 799/73 from which no lymph node biopsy had been obtained was interesting as the patient had a morphologic marker cell. This case is described below

The patient was a 71 year old man who had sought advice because of fatigue He had considerable enlargement of the spleen and mild generalised lymph node enlargement Hb 12 5 gram/100 ml platelets 32,000/μL Polyclonal increase of IgA normal IgG and decreased IgM The WBC was 8 800 with 24 % lymphocytes which were small with sparse cytoplasm and of normal nuclear structure 15 % of them had 2 nuclei or 1 deeply indented nucleus each lobe of which mirrored the other (fig.67) The laboratory assistant had not noticed the abnormality The bone marrow smear showed 40 % lymphoid cells. Of these more than 50 % had 2 nuclei and were of the same type as in the blood (fig 66) A few of them had a blast-like nucleus and occasionally visible nucleoli in both nuclear lobes Other bone marrow cells, also reticulum cells and plasma cells were normal. Owing to the fairly small increase in lymphocytes and the preponderantly mature appearance of them the examiner had regarded the bone marrow aspirate as normal. The patient received no treatment and died in a few days.

Necropsy showed generalised LLN In many sites incipient transformation to HL was seen (fig. 68) The bone marrow showed diffuse infiltration with the small "diplococcoid" cells A large percentage of the lymphoma cells in all infiltrates had a bi-lobed nucleus or 2 nuclei This applied both to the actual nodules, where the cells were larger and immature(fig. 69) and the internodular tissue where mature forms of lymphocytes corresponding to those in the blood were predominant (fig. 70) Many HL-cells had distinct 2 lobed or double nuclei and some closely resembled Reed Sternberg-cells (fig. 71) This can however be seen in all HL-cases and its significance can be questioned

Two years before death the patient had been admitted for anemia investigation. No palpable organ enlargement was found then The bone marrow and the blood picture was normal with a normal percentage of lymphocytes and no "diplococcoid" cells were found despite a careful review of these smears.

The cells in the blood thus were of normal appearance apart from the abnormality of nuclear shape The actual lymphoma nodules and a small part of the bone marrow cells were immature The internodular tissue in the lymphomas was of mature type but with a considerable percentage of "diplococcoid" cells. The binucleate lymphoma cells in the nodules and the mature internodular cells and those in the blood were probably genetically related The findings suggest that the internodular

tissue in the nodular lymphomas also consist of abnormal cells though often mor phologically without immaturity or atypia One might also conclude that a moderate number of cells may be shed into the blood in a patient with normal WBC and that they may have a normal appearance though they belong to the tumour population At least the cytologic abnormality if any may be very subtle.

Case 413/61 will also be described as it was the only one in group 3 where a diagnosis of macroglobulinemia was considered The patient, however had a monoclonal IgG-component Six years before being admitted to hospital the patient had had obscure abdominal pain and the blood values at that time had been normal, as had the E.S R The patient now was admitted for investigation of anemia Hb 5 6 gram/100 ml Overt hemolysis. Coombs test was positive WBC 6 500 with 75 % lymphocytes. Platelet count 114 000/µL Electrophoresis showed background immunoglobulin of 0.33 gram/100 ml and an M-component of 1 1 gram/100 ml of type IgGK (classification controlled and correct) The spleen was slightly enlarged no lymph nodes were palpable The bone marrow aspirate was poorly cellular with a predominance of lymphocytic cells, often in clusters They varied in size and shape and most had a fine chromatin net but few demonstrated visible nucleoli (fig. 105) Abundant mast cells and numerous plasma cells with a normal morphology Large amounts of hemosiderin pigment The picture thus resembled macroglobulinemia, but no transitional forms between plasma cells and lymphocytes were seen and the lymphocytes were subtly different from those in a classical case of macroglobulinemia

The patient was treated with corticosteroids with a moderate effect on hyper hemolysis but blood transfusions were necessary and the platelet values successively decreased The WBC rose slowly with an increasing percentage of "atypical" lymphocytes Maximum 10 800 with 92 % lymphocytes

Splenectomy was done after 19 months without any notable effect. The spleen weighed 480 g and had almost empty malphigan corpuscles and the red pulp showed a sparse lymphocytic infiltrate After splenectomy the M-component divided into 2 both of IgG-type They had concentrations of 1 13 and 1 56 gram/100 ml. The patient died 5 months after the splenectomy 2 years after diagnosis of thrombocytopenic haemorrhages

The picture of the bone marrow in sections obtained at necropsy was difficult to distinguish from that in macroglobulinemia diffuse but fairly sparse infiltration of lymphocytic cells abundant plasma cells and mast cells diffusely scattered in the lymphocytic cellular flora All lymph nodes were atrophic and no lesions whatsoever were found in them. The liver showed portal fibrosis with lymphocytic infiltrates of considerable dimensions

From a morphologic point of view the diagnosis of macroglobulinemia was considered in this case However no plasmacytoid cells with morphology intermediate between plasma cells and lymphocytes were seen Also the lymphocytic cells were more atypical and had less coarse nuclear structure than what is commonly seen in macroglobulinemia Because of this the case was referred to group 3 Probably it should be classified as LLD-3 but the absence of lymph node lesions makes it impossible to place in the lymph node classification scheme It is evident that tumour

of the lymph nodes need not be an obligatory component of such processes (This case is not included in the necropsy series of LLD 3)

Three of the cases in this bone marrow group were judged as undifferentiated lymphoma in the lymph nodes. These cases will not be further dealt with in the necropsy material but they are described below

Case 878/64 was examined 1 month before death. She then had a leukemia with WBC 282,000 with a preponderance of lymphocytes some atypical. The majority of cells were quite mature however and the blood picture was certainly of lymphocytic type (fig. 111) The bone marrow however was dominated by blastic cells without evident lymphocytic features (fig 110) This patient had had a lymphoma in the anterior mediastinum for 50 months. A biopsy of the lesion had been obtained at the time of diagnosis and had been interpreted as "lymphosarcoma" Review demonstrated undifferentiated lymphoma with a monomorphous picture of small, blastic cells. The necropsy specimens showed the same kind of infiltration

The case illustrates that the leukemia of undifferentiated lymphoma may be quite lymphocytic in type As cells from the blood contaminate the bone marrow smear there will be a mixture of blasts and lymphocytic cells, giving a confusing picture

In case 841/73 the bone marrow picture was similar The patient survived only some days after diagnosis and had occasional atypical lymphocytes in the blood

Case 633/68 had a bone marrow picture which was dominated by small lymphocytic cells with rather coarse nuclear structure Also larger blast like cells with sparse cytoplasm were present however (fig. 109) There was no distinct division into generations but a continuous anisokaryosis. WBC 3 500 with 59 % "lymphocytes" and 15 % "blasts" The patient died after 2 months without therapy The spleen liver and kidneys showed extensive infiltrates of quite undifferentiated blastic cells. The nodes were moderately enlarged and were dominated by similar cells. In many places there was a pattern suspected of nodularity Possibly the case represents a transitional form between nodular lymphoma and undifferentiated lymphoma.

DISCUSSION OF BONE MARROW SMEARS

The bone marrow picture described as group 1 corresponding to the lymph node picture of LLD-1 is always correlated with the hematologic picture of CLL. In practice these pictures of the marrow and lymph nodes are never seen in aleukemic disease It is possible that an occasional case of incipient CLL may show these pictures of the tissue without a leukemic blood picture but in this phase the disease is rarely investigated

The picture of the lymph node in LLD-2 is presumably always associated with the hematological picture of prolymphocytic leukemia. This sometimes, but not always applies to the bone marrow picture of group 2

Groups 1 and 2 are characterised by 2 easily distinguishable types of cells, the mature lymphocytes and the prolymphocytes. The cytologic picture in group 3 is more polymorphous. Separate generations are not readily distinguished but there is a continuous dyskaryosis and anisokaryosis. Generally the technical quality of the smears is poorer than in LLD-1 or LLD-2 This may in part be the explanation of the difficulty of separating LLD-3 and LLD-4 and undifferentiated lymphoma. Generally cellular and good smears are obtained only if the patients are leukemic. It may

appear strange that it is difficult to distinguish between LLD-3 and LLD-4 or undifferentiated lymphoma Clinically these conditions are very different With highly cellular and technically perfect smears it should be possible to estimate the percentage of pure blast cells and if this percentage is high the case probably belongs to the undifferentiated group It should however be pointed out that also in this group a large percentage of the bone marrow cells may be small and seemingly mature lymphocytes, even if they are atypical. The blood picture in leukemic cases of undifferentiated lymphoma is not necessarily blastic In some cases of undifferentiated lymphoma there may be a slight tendency to nodularity in the nodes and it may be a sign of a relation between these diseases. There is a possibility that the nodular lymphomas may progress to undifferentiated forms but this needs further study in larger materials If this is so it could be the explanation of the difficulties in distinguishing undifferentiated lymphoma and LLN or LLD-4 from the bone marrow pictures.

LLD-3 is astonishingly polymorphous in the bone marrow and here it is easier to confuse the picture with LLD-4 or undifferentiated lymphoma while it is easier to confuse LLD-3 and LLD 1 in the lymph node histologic picture Generally there is a higher percentage of cells with condensed chromatin in LLD-3 and a lower percentage of cells with very immature nuclei than in undifferentiated lymphoma Also the cases generally have a high percentage of plasma cells in the marrow but they appear morphologically normal and cannot be used as a reliable criterion for the assignment of a case to this group The prolymphocytes are not a characteristic feature of the bone marrow picture of LLD-3 though occasional such cells can generally be found

The most characteristic feature of the bone marrow cells in LLD-4 and LLN is the highly wrinkled or notched nuclear shape In some cases, this feature may not be very pronounced however and it did not appear meaningful to try to demonstrate the differences between LLD-3 and LLD-4-LLN objectively An experienced examiner will probably be able to guess to which group the case belongs, but it is nevertheless recommended to obtain a biopsy specimen of the lymph nodes in cases with atypical bone marrow cytology

It is occasionally uncertain whether a case should be assigned to group 1 or group 3 Clinically they may resemble LLD-1 or LLD-3 Biopsy specimens of the lymph nodes were missing in the doubtful cases in this series for which reason it is not possible to know whether such a specimen would have helped to classify the cases. In 2 cases however IF were seen in necropsy specimens and these cases should therefore presumably be referred to LLD 1 Such cases difficult to classify suggest that there are close connections between the various lymphoma groups. It might be questioned whether it is of any practical value to distinguish between LLD-1 and LLD 3 in leukemic cases. Probably the prognosis is worse in LLD-3 once the leukemia has appeared however The doubtful cases are relatively few compared to the whole material

Schwartz et al (63) used the term acute and chronic lymphosarcoma cell leukemia. Acute lymphosarcoma cell leukemia probably corresponds to leukemic cases of LLD-4 or LLN and possibly also cases of undifferentiated lymphoma with a

lymphocytic blood picture Chronic lymphosarcoma cell leukemia probably corresponds to LLD-3 in leukemic phase and possibly also some cases of LLD-4 or LLN If the term lymphosarcoma is omitted from the nomenclature,lymphosarcoma cell leukemia should not be used either As a name I suggest lymphoma cell leukemia with specification of the type of lymphoma in question in the nomenclature system used. For a full classification of a given case lymph node biopsy will thus generally be necessary

Chapter 6

NECROPSY MATERIAL

Sixty patients in the Malmö series were not examined with either biopsy of a lymph node or bone marrow aspiration These cases are therefore generally classified only on the basis of necropsy findings. Some cases, however were classified on biopsy material from other organs than nodes or bone marrow

Nodular lymphocytic lymphomas can readily be diagnosed in necropsy specimens Small-cell processes, such as LLD 1 LLD-3 and small-cell LLD-4 may be difficult to distinguish because of autolysis and cell swelling or shrinkage Prolymphocytes are often difficult to discern because of the clumping of chromatin which may take place post mortem This is probably the chief reason why IF are sometimes difficult to detect in necropsy specimens Yet there are generally parts of the infiltrates that are sufficiently preserved to allow classification, if many tissue blocks are examined

The cases were classified as follows

LLD-1	45
LLD-2	2
LLD-1 (+2)	1
LLD-3	2
LLD-4	2
Status after LLD-4	1
LLN + HL	1
LLN + D	5

This classification calls for commentation

The case "status after LLD-4" had a tumour of the tonsils verified by biopsy 13 months before death. It was of the small-cell type with very few blasts No new manifestations appeared after radiotherapy The patient died from arteriosclerotic disease and at necropsy no signs of tumour were seen. The case showed that processes of this type can occur as solitary lesions.

Of the cases LLN + D the diagnosis in 2 was made at necropsy of patients in whom the disease had not been suspected during life Both were aleukemic Two others, also aleukemic had been clinically misinterpreted as other malignant tumours (pancreatic carcinoma and mesothelioma of the pleura) In none of these 4 cases was the bone marrow involved The 5th patient had a lymphoma diagnosed intra vitam. Four months before death the epipharynx was found to harbour a tumour of LLD-4-type One week before death "blasts" (67 %) appeared in the blood when the WBC was 9 900 At necropsy LLN + D was found in many organs including the bone marrow as well as extra-lymphatic tumours.

The case LLN + HL (737/69) was interesting A 65-year old man who died from myocardial infarction At necropsy a walnut-sized submucosal gastric tumour was

found, which was LLN without signs of HL (fig. 107) Further a somewhat smaller tumour in the spleen. It was also microscopically nodular and built up of central HL foci surrounded by brims of lymphocytic lymphoma (fig. 108) The appearance gave the impression of HL starting in LLN The spleen was otherwise normal as were all other organs. This tumour had probably developed as a HL in the spleen if the patient had survived longer and the tumour process would probably have spread like HL. Such small lesions in internal organs are rarely if ever discovered intra vitam The findings suggest the possibility that tumours diagnosed as HL may have had a concealed pre-stage as LL.

The extent of lesions in the cases of LLD-4 and LLD-3 is given in table 11

LLD-4	Bone marrow	Spleen	Liver	Nodes
1042/70			+	RP
706/71	Focal		+	RP
LLD-3				
690/60	Focal	+	+	RP
290/70	Focal	+	+	All LL or HL see text

Table 11 Cases of LLD-3 and LLD-4 in necropsy series. RP = retroperitoneal nodes.

Case 290/70 (see table 11) had the first symptoms from HL in nasal polyps. LL was not diagnosed before necropsy The case is reported later

Two cases were judged as LLD-2 (1305/64 and 929/61)

1305/64 was a woman, aged 78 at death. She lived for 45 months after the diagnosis The WBC was high 200 000-300 000 with a varying percentage of "lymphoblasts The liver and spleen were markedly enlarged as were the lymph nodes. The patient was troubled by back pain. At necropsy alternating osteolytic and osteosclerotic changes were found in the vertebral bodies and also fibrous areas with lymphocyte infiltration Massively hyperplastic myelopoiesis and increased megakaryocytes. In the lymph nodes small necroses were seen with histiocytic infiltration and also calcification. The findings thus resembled those in other cases of LLD-2 described earlier

929/61 was an 89 year old man who was aleukemic He died from gangrene of the leg. The diagnosis was not made before necropsy The bone marrow showed focal infiltration. All nodes were engaged with lesions of type LLD-2 Here then was another aleukemic case with this picture of the lymph nodes.

In one patient the disease had been diagnosed intra vitam as CLL with "a blastic crisis"

This is the only patient in the series who had shown a blastic transformation in the sense of a fairly abrupt change in the clinical condition and cytologic picture of the blood The patient was a 63-year old man who had fallen ill with pneumonia WBC 23 000 with 75 % lymphocytes No enlargement of internal organs. Low immunoglobulin values. After treatment of pneumonia he first improved but one month before death his general condition suddenly deteriorated The WBC rose abruptly and the differential count showed 50 % "blasts" (slide not available) and 50 % neutrophil leukocytes. The patient died 3 months after diagnosis and necropsy showed focal bone marrow infiltrates. Most lymph nodes exhibited a picture assigning the case to LLD-1 though IF were not easily recognized The mediastinal nodes showed immature cells diffusely mixed with small lymphocytes without distinguishable IF thus a picture resembling LLD-2 (fig. 106) The immature cells were negative in chloracetate-esterase reaction and there were no other signs of a possible myeloblastic leukemia This case thus resembled a true "blastic crisis" of a CLL. Nothing further can be concluded from this single case about this type of the course of the disease

Of the 45 cases judged as LLD-1 there were adequate clinical examinations in 36 They were all leukemic at the time of diagnosis. Twenty-three of them had died from lymphoma disease 13 from some other condition. The average age at death of the 23 was 76 years thus roughly the same as in the patients from whom biopsy specimens had been obtained

The immunoglobulin values in the CLL-cases are summarised in table 14 One case had initially high diffuse values, which afterwards fell to low levels and afterwards rose again This increase was accompanied by the appearance of Bence Jones proteinuria In addition 3 monoclonal immunoglobulin components were found including 2 in the form of kappa-chains in the urine the 3rd as a small IgMK in the plasma Coombs test was positive in 2 of 15 cases examined.

The necropsy findings in these 36 cases showed generalised lesions in all except 5 in which one of the lymph node sites was without diagnostic lesions. Changes in the bone marrow liver and spleen were found in all. In none of the cases were any extra-lymphatic lymphoid tumours found One had HL one Hodgkin s disease These cases are described later

Two had myocardial amyloidosis of the senile" type (75 and 87 years old)

A further 9 cases were apparently CLL The clinical examinations were incomplete Five had increased WBC without any differential count in 3 no blood values were noted All the patients had generalised lesions without extra-lymphatic tumours One of the patients had died from generalised zoster with adrenal necrosis without any known preceding ill health.

One patient (90 71) a 91 year old man who had died from pneumonia had 9,500 WBC No differential count Necropsy had shown moderately wide-spread focal bone marrow infiltrates and slightly enlarged lymph nodes retroperitoneally They showed a picture that would fit in well with LLD 1 and suspect IF Other lymph nodes were not enlarged and showed only suspect pathologic changes. The

liver and spleen appeared normal. This case was probably an instance of "aleukemic CLL" in which the patient had died so early in the course of the disease that diagnostic general changes had not had time to develop. However, the bone marrow and at least one lymph node site were involved. It is not known whether the patient had absolute lymphocytosis but the WBC was not increased with certainty.

For practical reasons LLD-1 of the biopsy and necropsy series and bone marrow group 1 will henceforward be referred to as LLD-1 without specification.

It is evident that there are differences in the prevalence of the lymphoma groups in a series of lymph node biopsy specimens and a necropsy material. The chief reason for the lower frequency of LLD-1 in the material of lymph node biopsies is, of course, that biopsies are not often obtained in clinically characteristic cases of CLL. Cases of prolymphocytic leukemia are probably more prone to be biopsied because of the alarming blood picture. As has been pointed out earlier, it may be difficult to distinguish LLD-1 from LLD-2 in necropsy specimens, because of postmortal changes. Generally, IF can be detected in some tissues at necropsy of LLD-1, but if autolysis is pronounced, it may be rather difficult. In such cases with poor preservation of the cytological picture it is not recommended to try to distinguish LLD-1 from LLD-2 in necropsy specimens. Thus, an occasional case in this series may be incorrectly classified, though the 2 necropsy cases judged as LLD-2 were well preserved.

Some uncertainty also may pertain to the classification LLD-1 or LLD-3 in cases where IF are difficult to detect for technical reasons. The plasma cells, which are easily found in LLD-3 but very sparsely in LLD-1, are generally easy to find also in necropsy specimens, however, and it is felt that the separation of these two processes can be made in necropsy specimens with reasonable accuracy. Why, then, is the picture of LLD-3 so rarely met with in necropsy specimens? I think that this is best explained by the assumption that a high percentage of cases with LLD-3 transform to HL before death. The early phase of LLD-3 is probably often an asymptomatic disease and in many cases of HL diagnosed at necropsy or biopsy LLD-3 may very well have existed for a long time without affecting the health of the patient.

As has been pointed out in chapter 4, the demarcation between LLN and mixed histiocytic lymphocytic nodular lymphoma is somewhat arbitrary, for which reason comparison of the frequency of nodular lymphomas with other statistics is uninteresting. The group of nodular lymphomas as a whole is the largest in the nodal non-Hodgkin's lymphoma series of the institute at present. In the material of cases diagnosed at necropsy the nodular lymphomas are not very frequent. This also may be taken as a sign of a transformation to HL before death in a large number of such cases. It is also my impression that undifferentiated lymphomas are diagnosed much more frequently in necropsy material than in biopsy material. This may possibly be a sign of other types of lymphoma developing an undifferentiated cytologic picture before death. The nodular lymphomas and the undifferentiated lymphomas, however, were not studied as groups in this material and this point will not be further dwelt upon.

DIAGNOSIS	NUMBER ALL (M/F)	DIED OF LYMPHOMA ALL (M/F)	MEAN AGE AT DEATH OF THOSE WHO DIED OF LYMPHOMA YEARS ALL RANGE (M/F)	MEAN SURVIVAL OF THOSE WHO DIED OF LYMPHOMA MONTHS ALL RANGE (M/F)
LLD 1	94 (62/32)	57 (42/15)	74 50-88 (74/75)	45 0-180 (44/47)
LLD /Group 2	12 (7/5)	10 (6/4)	74 53 92 (72/76)	36 0 148 (37/35)
LLD	9 (5/4)	6 (3/3)	67 58 84	52 7 137
LLD 4	15 (11/4)	13 (9/4)	65 35-84	44 7 126
LL[illegible]	13 (7/6)	11 (5/6)	69 52 95	24 0-70

Table 1[illegible] Total material. Cases of macroglobulinemia and doubtful classification not included

Certain data on the entire necropsy material are given in tables 12 and 13 Broadly speaking the figures agree with the smaller biopsy material. All the groups showed a shorter average survival because they included the cases that were diagnosed at necropsy and those in which the patient did not seek advice until the disease was advanced and who died soon after the diagnosis Most of them probably had had symptoms for some time but it was often not possible to say anything certain from the preliminary notes made on admission of the patients and no attempt will be made to analyse the figures. The smaller groups are not sufficient for statistical significance and the survival figure for LLN for example is misleading as in 3 of the patients who died of lymphoma the disease was not diagnosed as such before necropsy and nothing is known about the previous clinical history of the patients If the figures of age at death of those who died of lymphoma are judged in relation to the roughly estimated survival figures given in chapter 4 it seems probable that LLD-3 generally starts somewhat earlier than LLD-1 or 2 It also appears probable that LLD-4 and LLN may occur in younger patients than LLD 1 2 or 3 But they are also seen in extremely old people

	Range	Percentage > 60 years
LLD-1	48-92	92
LLD-2/Group 2	52 88	92
LLD-3	53-83	56
LLD-4	33-86	60
LLN	47 95	69

Table 13 Age at the time of the diagnosis in total necropsy series

The longest survival time in the entire material was that of a man in bone marrow group 1 3 who fell ill at 43 years and lived for a further 246 months.

The age at the time of diagnosis is given in table 13 The youngest in the CLL group was a woman 48 years. Three in this group lived for more than 10 years after the diagnosis, 12? 160 and 180 months.

In all the groups the majority of the patients were males The sex distribution cannot be judged with anything like certainty from the figures in the small groups. LLD-1 is probably twice as common in men as in women LLD-1 is primarily a disease of old people and from a statistical point of view shortens the expectancy of life but little

In 34of 94 in the LLD-1 series clearly malignant tumours of non-lymphatic type (basal cell epithelioma and latent prostatic carcinoma and myeloma included) were

diagnosed during the course of the disease or at necropsy Of these 7 had more than one type of tumour histologically In addition 2 had hypophyseal adenoma and 4 meningoma

If we add LLD-1 bone marrow group 1 3 and LLD-2/bone marrow group ? it will mean 110 cases. These groups probably approximately correspond to cases generally included in series of CLL in the literature 41 of 110 had clearly malignant tumours (including the above) of non-lymphatic type i.e., 37 % Owing to the small figures, it is meaningless to count the various types of tumours separately The overall frequency does not exceed that of the material of the department of pathology as a whole(in a large material from approximately the same period 38 % of necropsied cases had carcinomas (7)) Space will not permit analysis of the figures. In LLD-3 the only non lymphatic malignant lesion was Bowen s disease in case 855/67

In the LLD-1 series 15 had zoster on some occasion during the course (16 %) Zoster also was seen in one patient in group 2 one in group I-3 and one in LLD-3 One of the macroglobulinemia patients (chapter 8) also had zoster In LLD-4 and LLN altogether 28 cases zoster had been noted in 3 patients, all of whom had low immunoglobulins.

In LLD-1 there was one case of progressive multifocal leukoencephalopathy one of necrotising cytomegalic virus infection in the adrenals one with large amounts of recurrent mollusca contagiosa one pneumocystis carinii pneumonia one toxoplasma myocarditis and one listeria meningoencephalitis No such infections were found in the other groups.

Pulmonary mycosis was seen in one case of LLD 1 one case of bone marrow group 2 and one case of LLD-3 Active tuberculosis of the lungs or other organs was found in 6 cases of LLD-1 including 2 with fatal miliary tuberculosis. Tuberculosis was also found in one patient in bone marrow group 2 and one in LLD-4 (high immunoglobulins) One of the LLN patients had renal tuberculosis of long standing the only case in the series where the tuberculosis was diagnosed intra vitam Tuberculosis was at least as common during the latter part of the period as in the former part and is obviously still a serious risk in patients with lymphoma and lymphatic leukemia

The immunoglobulin values are given in table 14

In LLD 1 there was one patient with myeloma (not included in the table) of IgG type In addition to this case 11 monoclonal immunoglobulin components, all probably of IgM type were found in all together 77 patients who had been examined some time in the course of the disease

In bone marrow group one monoclonal component (IgM) was found

In group 1 3 (4 examined) had low immunoglobulin values early 1 normal 1 high Two mono lonal components were found both IgGK

In LLD 3 4 patients had monoclonal immunoglobulin components on some occasion Two of them were found only in the urine as light chains one kappa and one lambda In on ase it was a question of an IgG in the serum and in one case an IgM in the serum

One of the cases of LLD-4 had a small component in the serum electrophoresis in β not examined further

One of the patients in LLN had an IgGL monoclonal component in the serum electrophoresis

Diagnosis	Number of cases examined	Low	Normal	High
LLD-1				
Early	74	44	21	9
Late	47	38	5	4
LLD-2/Group 2				
Early	8	4	2	2
Late	6	5	0	1
LLD-3				
Early	5			5
Late	7	1	2	4
LLD-4				
Early	11	5	4	2
Late	11	6	2	3
LLN				
Early	5	1	3	1
Late	7	4	2	1

Table 14 *Immunoglobulin findings in total material*

Chapter 7

MACROGLOBULINEMIA SERIES

This chapter concerns all cases with a clinical diagnosis of Waldenström s macroglobulinemia In 5 of the Malmö-cases the bone marrow was examined and the findings were of the "classical" type and have been described under group 4 in the chapter on the bone marrow material. A further 2 cases in the Malmö-series had this clinical diagnosis. In one (V 434/71) there was no bone marrow examination, in one (99/62) the picture of the bone marrow was of different type described below Two cases not belonging to the Malmö-series are included in this chapter They also had Waldenström s macroglobulinemia diagnosed clinically

All these 9 cases are the subject of this chapter Three had peculiar features the remaining 6 will be treated first They had a picture of the bone marrow smears of classical type Four of the patients were women 2 were men The age at death ranged from 49 to 92 years and the survival time from the diagnosis from 49 to 180 months (average 92 months) The youngest patient at the time of onset (33 years) and the one who survived longest (about 15 years) was a woman (777/68) who eventually died from HL. The M-components were of type IgM in all. Light chains were typed in 3 Two were kappa and one lambda The highest concentration varied from 2.3 to 9 0 gram/100 ml Case number V 251/73 had 2 M-components, IgMK with maximal concentration of 2 3 gram/100 ml and IgGK with a maximum concentration of 1 5 gram/100 ml. The patient was thought to have macroglobulinemia + myeloma but the skeleton was normal roentgenographically and the morphologic picture was that of macroglobulinemia

At the time of the diagnosis one of the patients had a normal hemoglobin concentration one had severe hemolytic anemia the others moderate non-characteristic anemia One had thrombocytopenia The patients sought advice for various reasons one because of zoster one because of nose bleeding one because of joint pain one because of tingling of the fingers and one because of fatigue One was discovered incidentally at check examination of the E.S R at the department of geriatrics

At the time of diagnosis none of the patients had palpable enlargement of lymph nodes liver or spleen. Only in 777/68 was such enlargement discovered in the course of the disease (due to HL) None of these patients had ever had absolute lymphocytosis of the blood All had considerable monocytosis on some occasion 2 of them almost constantly One patient died after 16 months from myocardial infarction 777/68 died from HL after 180 months ?04/69 died after 100 months of influenza during an epidemic The patient was in a good clinical condition and the M-component had been falling continuously during treatment with melfalan The other 3 patients died mainly from old age 80 90 and 9? years old

Two of the patients received no specific treatment (survival 146 and 49 months) The others were treated with cytostatics during some period and three of them also received corticosteroids.

FINDINGS AT NECROPSY

204/69 who died from influenza had insignificant focal lymphoplasmocytic infiltrates of doubtful diagnostic significance in the bone marrow All the other organs were entirely free from infiltration The mediastinal lymph nodes showed a striking immunoblastic reaction after influenza pneumonia of the same appearance as in many other immunologically normal patients who died in that epidemic.

The other 5 patients showed bone marrow infiltration of diffuse type with the same forms of cells as in the aspirates obtained during life Infiltration was never entirely compact but a varying number of fat cells persisted as did hematopoietic cells.

These patients had insignificant changes in the spleen. The weight of the spleen varied from 90 to 260 g. The changes in all of them had the character of a sparse diffuse deposition of lymphocytes, plasma cells and intermediate forms in the red pulp while the white splenic pulp was not expanded. Mast cells were irregular components of the extramedullary infiltrate and especially in the spleen they were often difficult to detect.

The liver showed insignificant infiltration in the portal tracts in 2 patients but without enlargement of the liver Four of the 6 thus had no liver changes.

As pointed out above, the lymph nodes in 204/69 were of normal appearance The remaining 5 had microscopic changes in the lymph nodes. All of the lymph nodes were involved though the involvement of the inguinal and axillary nodes were generally of dubiously diagnostic character In one all the lymph nodes were of normal size in 3 slightly enlarged in 777/68 markedly enlarged by HL (see below) The picture of the lymph nodes was characterised by infiltration of lymphocytes plasma cells and intermediate forms in the cortex and medulla but not so dense as to obliterate the sinuses. Often there was a diffuse division into fields with alternating small, lymphocyte-like and larger plasma cell-like forms (fig 87) the latter tending to be situated adjacent to the sinuses. The sinuses often contained abundant phagocytes, very often with phagocytosis of red blood cells Deposition of iron was common within and around the sinus. Mast cells were seen along the sinuses and vessels, but were not with certainty more abundant than in reactive lymph nodes. No germinal centers were seen. The capsule and the pericapsular tissue always showed a certain infiltration somewhere but not necessarily in each lymph node site A remarkable feature of this disease was that the infiltration in the perinodal adipose tissue tended to accentuate the lobular architecture of the fat in a way not seen in LLD-1 or other lymphocytic lymphomas. The appearance was so characteristic as to warrant assumption of macroglobulinemia. When the infiltration became more dense the lobular appearance became more compact which could be misinterpreted as nodular lymphoma (fig. 89) It was not only cachectic patients with accentuated lobulation of the adipose tissue that showed this sign but also patients in a good nutritional state The phenomenon is presumably due to a tendency of the infiltrates to follow the lymphatic vessels and often they were dilatated which

per se tended to accentuate the lobulation (fig 90)

777/68 had HL in the inguinal and paraaortic lymph nodes. After a course of almost 15 years, during which she had received about 4 8 g chlorambucil and corticosteroids (for details see 82) she deteriorated rapidly within about half a year At the same time she had increasing swelling of the legs The concentration of the M-component had for 2 years been decreasing Necropsy showed fist-sized sarcomatous lymph nodes inguinally and in the pelvis and retroperitoneum Microscopically they showed HL (figs. 96 97) The bone marrow and other nodal sites still showed infiltration of the same type as in the bone marrow aspirates (figs. 98 99) The sarcomatous lesions also showed amyloid deposition (fig. 100) which were not seen in other organs. It might be mentioned that none of the other patients with macroglobulinemia showed amyloidosis and neither did any of the other patients with lymphoma in the entire series (besides 2 LLD-I with senile" heart amyloidosis)

In no case did the lymph nodes show typical IF However there were always scattered immature large cells with "vesicular nuclei and large nucleoli (figs. 88 91) The nucleus was generally irregular in shape monocytoid" and the cytoplasm abundant These cells often were in mitosis. They were rarely found outside the nodes and spleen

777/68 had alternating areas of small-cell type in the lymph nodes and areas with such large cells. These foci showed mitotic figures often atypical and gradual transition to HL (figs. 96 97)

V 251/73 (with M-components) showed no signs of myeloma at necropsy

The kidneys and renal pelvic fat tissue in 4 of these patients showed lymphocytic infiltration with a similarity to that of LLD-I but the infiltration had a stronger tenden y to spread along the small vessels and the collecting tubulus in the medulla and the upper part of papillae One of the patients had a massive infiltrate in the mucosa of the renal pelvis which was markedly thickened

In cases the lungs showed sparse infiltration peribronchially One had marked interstitial infiltration in the myocardium Another had an infiltrate in the pericardial fat No extra-lymphatic tumours were found in the group

THREE CASES WITH A CLINICAL DIAGNOSIS OF MACROGLOBULINEMIA EXHIBITED DEVIATING FEATURES 99/67 had a short history (2 3 months) of increasing fatigue and headache Admitted almost comatose He had an IgM-component of 6 gram 100 ml WBC 9 700 with __ % cells judged as "atypical plasma cell like lymphocytes and 8 % "atypical monocytes" Platelet count normal, Hb 13 0 gram 100 ml The bone marrow aspirate was highly cellular but difficult to interpret because of a heavily stained protein film which covered all the structures. The nuclei were roughly twice the size of that of lymphocytes and had blast-like characteristics They contained abundant inclusions which stained PAS-positively like the film (fig 103) Many of the cells had a very narrow rim of basophilic cytoplasm others clearly plasma cell-like features with abundant basophilic cytoplasm but always more immature nucleus than ordinary plasma cells (figs 101 102) The patient had magnificent retinal changes of macroglobulinemia-type and developed renal insufficiency which was interpreted as due to hyperviscosity No skeletal

lesions were demonstrable in the roentgenogram. Treatment with melfalan was started, but the patient suddenly died 4 days later The cause of death was a ruptured aneurysm of the superior mesenteric artery At necropsy the bone marrow showed small diffuse aggregates of plasma cell-like elements with intranuclear PAS-positive inclusions in virtually every cell (fig 104) The nuclei were sometimes perforated by a large number of such small inclusions. No mast cells were seen Plasma in the vessels was intensely PAS-positive There was no arteriosclerosis of the cerebral arteries, but the brain was studded with haemorrhagic micromalaciae. In the red pulp of the spleen there were single cells resembling those in the bone marrow but the spleen was small (90 g) and the liver was completely free from abnormal cells. The lymph nodes were of normal size and contained sparse pathological cells in the sinuses but none in the parenchyma.Marked erythrophagocytosis in the RES

This patient thus had a disease clinically characterised mainly be an uncommonly malignant hyperviscosity a large M-component and a quantitatively insignificant infiltrate in the bone marrow but morphologically different from the classical macroglobulinemia in that the picture was dominated by large cells with plasma cell like cytoplasm, but a blast-like nucleus. The large amount of intranuclear PAS-positive inclusions in practically all cell nuclei did not resemble the classical picture of macroglobulinemia either The larger forms of cells resembled to a certain extent the cells in LLD 2 There were abnormal cells in the circulation The variation in the cellular picture was clearly different from myeloma There were no osteolytic foci.

1224/70 This patient sought advice because of inguinal hernia. Examination revealed a WBC of 120 000 and a high E.S.R and M-component. A bone marrow aspirate at another hospital (smear not available) was described as "well compatible with macroglobulinemia" The blood picture was described as "small-cell CLL" The patient was treated with prednisone and chlorambucil without any notable effect and the WBC showed a tendency to increase She complained of fatigue and frequent bleeding of the nose and gums. Because of thrombocytopenia and anemia a moderately enlarged spleen (19 x 11 x 6 cm) was removed after 20 months. The patient died from pneumonia after the operation

At splenectomy also a lymph node was removed from the abdomen. It was moderately enlarged and showed a picture fitting in well with macroglobulinemia as described in the section on clinical typical cases. No IF Open sinuses. The diffuse chess-board like distribution of large and small cells was clearly seen (fig. 87) and some blastic forms were found diffusely in the tissue (figs. 88,91) The spleen showed well preserved Malpighian corpuscles and dense infiltration of cells in the red pulp The cells were of the same type as in the lymph node There was a pea-sized focus with quite another structure which compressed the surrounding splenic parenchyma. The cells were large and polymorphous and there were numerous bizarre tumour cells with large nucleoli as well as mitotic figures (figs. 92 93) This tissue was of HL-type At necropsy all lymph nodes which were insignificantly enlarged showed the same picture as that of the lymph node extirpated in association with the splenectomy The liver was completely free from infiltration in the

portal tracts while the sinusoids contained numerous lymphocytes from the blood (WBC terminally 470 000) The bone marrow showed dense diffuse infiltration of predominantly lymphocytes but also plasmacytoid forms and mast cells thus a picture compatible with the classical type (fig. 86) The kidneys showed dense infiltrates in the medulla. No HL-changes anywhere at necropsy

What should this condition be called? Had the patient a CLL with a macroglobulin band in the electrophoretic pattern and not a macroglobulinemia in the strict sense of the term. In my opinion the picture of the tissue deviated so much from classical CLL and resembled classical macroglobulinemia so much that it is more correct to regard the condition as the latter disease The picture of the lymph node was typical. Lack of tissue infiltration in the liver despite a high WBC was not compatible with CLL. The bone marrow picture was compatible with macroglobulinemia On the other hand the blood picture was that of CLL. The diseases are probably closely related and further differentiation might seem less meaningful. It nevertheless appears reasonable that macroglobulinemia can sometimes occur in a leukemic form In the light of this consideration one might thus call the disease "leukemic macroglobulinemia" rather than CLL with macroglobulinemia The HL-changes in the spleen would probably have grown and similar changes probably have developed elsewhere if the patient had lived longer

V 434/71 sought advice because of cough and fatigue He dated the onset of his disease to an attack of influenza 18 months previously Chest X-ray showed diffuse "probably inflammatory changes and a large tumour in the lingula Cytologic examination of the sputum showed squamous cell carcinoma and treatment with cyclophosphamide was started as surgery was regarded as out of the question

The E.S R was 100 mm/1 hour and electrophoresis showed 3 M-components one IgMK of _ 45 gram/100 ml and one IgGK of 2 0 gram/100 ml and a small IgAK of) 42 gram 100 ml The concentration of the first 2 was found to be increasing at controls Bence Jones proteinuria type kappa The differential count showed neutrophilia and often monocytosis but never lymphocytosis. The bone marrow was not examined Treatment had no demonstrable effect on the lung changes and the patient deteriorated and died in a cachectic state after 14 months

Necropsy showed no carcinoma of the lung the tumour was instead built up of the same forms of cells as those forming widespread diffuse interstitial infiltrates of the lung These cells consisted of small lymphocytes and plasma cells and intermediate forms and "monocytoid" blasts There was a diffuse division into fields with lymphocytes and plasma cells separately but without any sharp line of distinction between the fields (fig 95) The bone marrow showed foci of the same cells with lymphocytes centrally and the plasma cell-like forms in marginal zones (fig 94) The spleen was slightly enlarged with mixed cell infiltrates in the red pulp while the white pulp appeared normal The liver was of normal size but showed sparse periportal infiltrates mainly lymphocytes The lymph nodes were also of normal size but showed a typical picture of macroglobulinemia described earlier Here too the lymphocytic and the plasma cell like forms were arranged in a chess-board fashion All the lymph nodes showed abundant atypical blastic forms but they were diffusely scattered and without any HL like proliferations

This case thus resembled mainly the "pulmonary" type of macroglobulinemia The presence of components of IgG and IgA-nature was a remarkable finding. All had kappa light chains The chess-board-like pattern of the distribution of the lymphocytes and plasma cells was very distinct and in the bone marrow foci plasma cells always formed marginal zones around the lymphocytes. It appears reasonable to assume that the lymphocytes differentiated into plasma cell-like forms and were thereby displaced towards the periphery of the foci. In this process they possibly changed their production of heavy immunoglobulin chains.

DISCUSSION OF MACROGLOBULINEMIA MATERIAL. Analysis of the bone marrow smears can evidently detect most typical cases of macroglobulinemia simply from their cytological characteristics. As mentioned elsewhere in this publication a cytologic picture resembling that of macroglobulinemia was occasionally seen in cases with another type of immunoglobulin production (case 413/61) Such cases are presumably rare Further it is obvious that cases with clinical macroglobulinemia may have a cytologic picture differing from the classical one (99/62) Further it is clear from what was said above that cases with large macroglobulin components and a tissue picture of classical macroglobulinemia may have leukemic disease resembling CLL (1224/70) and that clinically characteristic macroglobulinemia can develop into malignant lymphoma with quite another picture of the tissue (777/68)

Is Waldenström s macroglobulinemia, then, an entity distinguishable from other lymphoproliferative conditions? It is obvious that on electrophoresis small macroglobulin components may occur in lymphoproliferative diseases which do not resemble classical Waldenström s macroglobulinemia clinically But if one limits the diagnosis to cases with macroglobulin components with a higher concentration, the situation will be different It has been recommended to set the limit at about 1 5 gram/100 ml (see e.g. survey in 44) In the present material, however there were cases where the first determination showed concentrations of less than 1 gram/100 ml (891/69 0 74 gram/100 ml, later increasing) but where the morphology was that of classical macroglobulinemia Cases with macroglobulin components of this size may thus be examples of true incipient macroglobulinemia or of cases with lymphoproliferative disease of some other type If the concentration of the component *at the time of diagnosis is more than 1 5 gram/100 ml, the disease will most* often be of morphologically macroglobulinemia type In treated cases the concentration of the component may of course fall again with preservation of the picture of the tissue Presumably the macroglobulin is produced by the plasma cell-like forms in the bone marrow and probably also elsewhere in the tissues. Should these cells be regarded as neoplastic or are they reactive cell forms with production of antibodies against some unknown agent? If the immunoglobulin-producing cells are tumour cells, it would seem remarkable that the concentration of the M-component can fall in advanced disease with increasing infiltration of pathologic cells, or when the patient is affected by obviously malignant cell proliferation. A similar situation may be seen in multiple myeloma however when the monoclonal immunoglobulin component may decrease in concentration in spite of a rapidly expanding tumour mass The situation also can be compared to the few published cases of CLL where leukemia disappears with the appearance of HL (see later) Immunofluore-

scence studies of the sarcomatous growths in cases of macroglobulinemia reported in the literature argue against the production of immunoglobulin in such tumour cells (see chapter 1) The development of clearly malignant tumours terminally does not necessarily mean that the disease should be regarded as malignant from the beginning. Compare for example the well-known development of malignant lymphoma in immunodeficiency states. In my opinion however some of the features referred to above suggest that the disease should be regarded as a low grade malignant process from the very beginning Case 1224/70 obviously fills all criteria for leukemia and may thus by definition be regarded as a malignant condition Since the picture of the tissue was of macroglobulinemia type and not of CLL type I feel as previously pointed out that it is probably a question of a true leukemic macroglobulinemia Probably only the lymphatic cells have a strong tendency to be released in to the circulation while the plasma cells and the blast-like cells are bound to the tissues. A similar situation is seen in LLD-1 or LLD-3 where the blood morphology may be mainly mature while the tissue morphology may contain a high percentage of immature cells. The morphologic picture of a tissue may therefore characterise the disease better than the blood picture Another point arguing for the malignant nature of the disease is the atypical blast-like forms in the tissue infiltrates which are always found though in low percentage in early stages. They are probably analogous to IF-cells in CLL. It is probably these forms of cells that cause sarcomatous growths in the terminal phase The sarcomatous transformation seen in 2 of these 9 patients may have had a similar relation to these immature cells as HL had to IF-cells in LLD-1 If the IF-cells can become HL-cells having lost the capacity of lymphocyte production it is not unreasonable to suppose that on transition to HL the immature cells in macroglobulinemia lose their ability to produce macroglobulin-producing daughter cells The lack of demonstrable production of macroglobulin in tumour cells is therefore no proof against the assumption that the cells are related to the initial lymphocytic infiltration

The nature of the immature cells could not be studied more closely because of lack of suitable material. They resemble IF-cells, but have not the focal distribution of the latter and are more atypical in that the shape and chromatin structure of the nuclei are more irregular

The occurrence of cases with several M-components suggests that the disease attacks lymphocytic cells in transformation V 434/71 showed a very marked plasma cell differentiation and also had immunoglobulin components of both IgG and IgA type The occurrence of cases with macroglobulinemia like morphology but with M-component of another type might perhaps be explained as a condition where the transformation is so rapid that the macroglobulin-producing stage of the cells life is too short for any measurable concentration of macroglobulin to appear in the plasma This assumption may be strengthened by the absence of cells intermediate between lymphocytes and plasma cells in those latter named conditions.

The above speculations are not well founded because of the smallness of the number of cases in the series Despite the interest in macroglobulinemia and the numerous publications on this disease there is hardly any published series of cases

studied morphologically on different occasions during the course of the illness and further such series are desirable in order to get a better grip on the nature of the disease as it is evidently not uncommon that a change from "benign" to "malignant" takes place both clinically and morphologically

Clinically characteristic cases of macroglobulinemia have some morphological resemblance to LLD-3 in the nodes but the cytological picture is characterised by a series of cells with a smooth transition from lymphocytes to plasma cells. In LLD-3 such intermediate forms are not seen and the lymphocytic cell component is considerably more atypical. Lymph node tumours are not a feature of macroglobulinemia at least not in the early phases. Macroglobulinemia appears to be primarily a disease of the bone marrow

See further the discussion on nomenclature in chapter 12

Chapter 8

THE IMMATURE CELLS IN CHRONIC LYMPHATIC LEUKEMIA

1 IF IN BIOPSY MATERIAL. The investigation was confined to lymph node specimens. Sections of the bone marrow were available in only a few cases I have however a large number of bone marrow sections from cases of CLL that are not included in this material Judging from personal experience IF are rarely demonstrable in such sections and thereby confirm experience from the necropsy material (see below) In the marrow the immature cells are most often diffusely distributed. The immature cells described in bone marrow smears, however cytologically resemble IF-cells in the lymph nodes and are presumably of the same nature (figs. 8 9)

IF in lymph nodes vary widely in size and number They are often detectable even under low magnification (fig 1) and are always seen throughout the node with no difference between the peripheral and central parts. They are often of uniform size but can coalesce to form larger areas of immature cells. Sometimes however IF are small and one must search for the typical cells under high magnification. Occasional immature cells are found single in the mature parts. The IF are richly vascularised Sometimes one sees a wide capillary centrally in the IF sometimes a somewhat wider vessel of precapillary dimensions. Longitudinal sections of such vessels will occasionally show IF as vessel sheaths over long areas

IF contains at least 4 different types of cells (like LLD-2 which in every respect consists of the same tissue as IF though it is not focal but involves the entire node)

1 Mature lymphocytes. The percentage of such lymphocytes varies. The larger the IF the fewer such lymphocytes, but the smallest IF are so to say only a concentration of immature cells among mature lymphocytes and not well outlined foci.

Prolymphocytes They are generally the dominating cell.

3 Single very large cells with a diameter of at least 4-5 lymphocytes with abundant strongly basophilic cytoplasm and a nucleus without chromatin condensation and with one or several large nucleoli staining dark blue with Giemsa (figs. 7 187) These cells are very rare and far from every IF in every plane of the section contains such examples They increase in abundance with the size of the IF They are hereinafter called IF 1 cells.

4 The cells described earlier (chapter 4) and illustrated for example in figs 7 4 148 and 18 They are intermediate in size between IF 1 cells and prolymphocytes. The nucleus shows a certain chromatin condensation of lymphocyte-like type but always contains one large often centrally situated nucleolus staining light blue with Giemsa They are hereinafter called IF 2 cells Mitotic figures are seen in IF 1 and in IF cells, and in prolymphocytes

These 4 types of cells which I am inclined to interpret as 4 generations of the same form of cell are fairly well distinguishable from each other morphologically

but there is, of course a certain variation of the different forms of cells which occasionally makes it uncertain whether a given cell is IF 1 or IF 2 or whether it is IF 2 or prolymphocyte (see further chapter 10)

Are IF specific of CLL? It is clear from the preceding sections that IF occur practically only in cases with a leukemic blood picture A single case in this series showed suspect IF without clear leukemia of the blood (902/71 in chapter 6) This was probably a very early and certainly subclinical disease. Practically all of the cases with IF thus had the blood and bone marrow picture of CLL. Those cases called LLD-3 had according to definition not IF Many of them were aleukemic and they were cytologically more atypical than cases with IF Whether one should regard IF as exclusive of CLL is thus a question of definition. Leukemic LLD-3 may resemble the less atypical LLD-1 hematologically and morphologically intermediate cases suggest a close relationship But there are differences clinically if one regards the cases as groups. I have chosen to regard LLD-1 as representing CLL, and I have retained leukemic LLD-3 as a special group though I am well aware that many hematologists and possibly with equal right, would call both types variants of CLL. Typical IF are thus seen, according to this point of view only in CLL. But it is beyond doubt that also LLD-3 contains immature cells resembling IF-cells, though they do not form the characteristic foci of CLL. Aspirates, as pointed out earlier do not show the clear division of generations in these cases, and the mature cells are partly atypical.

An essential question is whether IF are constant structures or whether the picture can change between different nodes and from one time to another It is difficult to give a clear-cut answer to this question. IF were sometimes not detectable in necropsy specimens, even if the biopsy specimen of a lymph node in the same site had shown such foci. This probably had a technical explanation, viz. it was due to autolysis. One must thus resort to biopsy specimens Of the LLD-1 cases, there was more than one lymph node biopsy specimen with a picture of LL in only 2 cases, both of which clearly had IF on both occasions. In one of the biopsy cases 4 lymph nodes adjacent to each other were removed on the same occasion. All of them had IF In 2 of the LLD-3 cases there were later biopsy specimens that showed a picture of LL. IF were not seen None of the biopsy cases of LLD-3 showed IF in necropsy specimens. The findings in these few cases thus suggest constancy In those cases where repeated bone marrow smears had been obtained it was meaningless to try to assess the percentage of immature cells with accuracy owing to the varying dilution with blood I would assume that IF in lymph nodes and the percentage of immature cells in the bone marrow can vary from time to time though the material described provided no acceptable documentation. But both phenomena are probably always present to some extent in CLL.

The amount of IF does not appear to be directly related to the value of WBC in the peripheral blood When the extent of IF in biopsy specimens was graded subjectively into 3 groups, the following picture was obtained (fig. III)

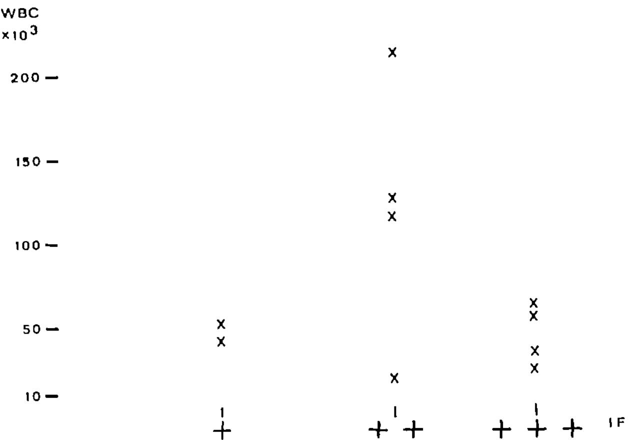


Fig. III Extent of immature foci in lymph node biopsy specimens from untreated patients.

Thus there was no direct relation between the distribution of IF in a given lymph node and the WBC However owing to the uncertainty of the representativeness of the biopsy specimen for all lymph nodes in the body this can hardly be taken as evidence that there is no such correlation. Only biopsy specimens of patients who had not been treated are included in fig. III In 3 cases treatment had been started before biopsy One of them that had received radiation to the region in question had the most extensive IF in the series and one lymph node with a picture in parts resembling LLD-2 with coalescent IF and a focus of HL (figs. 146 152) The WBC at the time of biopsy was 25 000 Two of the patients had received cytostatics and in one of them the WBC was normal the other had severe leukopenia but both had IF ++

2. IMMATURE CELLS IN THE BONE MARROW Seven of the bone marrow aspirates in group 1 had immature ++ They ranged from 20 000 to 600 000 in WBC at the time of aspiration with a mean of 190 000 In the 35 + cases it ranged from 11 000 and 295,000 (mean 85 000) The difference was statistically not significant. Also a number of patients in both series had been treated for a varying period be fore examination, which makes evaluation difficult.

The cases in the bone marrow series with immature +++ thus group 2 had at the time of aspiration a WBC of the same level as in group 1 with an average of 97 000 if the aleukemic patient be excluded As previously mentioned these patients might have had a greater tendency to reach very high WBC but the difference was by no means striking.

It is thus not possible to correlate immature cells in lymph nodes or bone marrow with the level of the WBC in the peripheral blood in this material

3 IMMATURE CELLS IN THE PERIPHERAL BLOOD If all patients with ++ or +++ in the peripheral blood (thus from groups 1 and 2) were pooled there would undoubtedly be a concentration of cases with very high maximal values of WBC, with an average of maximal values of 328 000 Of all these 10 cases, 6 had on some occasion more than 150 000 The difference from cases with + in the peripheral blood was however not striking at the time of the first investigation but only regarding the maximal values recorded.

"Prolymphocytic leukemia" according to Galton et al. (19) is probably the same as the cases in my series with a high percentage of immature cells in the peripheral blood (+++ or ++) Galton et al. defined their cases on the basis of the blood picture and not on that of the bone marrow Broadly speaking the series resembled each other Galton et al. wrote that splenomegaly was typical of their cases. In my cases it was impossible in retrospect from the clinical records to grade the enlargement of the spleen in an exact way but in at least 5 of 9 cases the spleen was described as very large but in 3 it was not palpable (1 case could not be judged because the spleen was covered by colonic cancer) But the lymph nodes were markedly enlarged in 6 of my 10 cases, while Galton et al. reported that enlargement of the lymph nodes was not striking in their series. Enlargement of organs at necropsy is difficult to evaluate because of the effect of earlier treatment The average weight of the spleen in my cases at necropsy was 1 020 g (one excluded because of scarring after infarction) (Galton et al. 1,383 g) In the bone marrow series the cases with + in the

peripheral blood (27 cases) had on the average a spleen weight of 600 g. Corresponding liver weights were 2 000 g (Galton et al. 2 445 g) and 1,910 g. It is, however not very meaningful to compare the values because several of the largest spleens had been irradiated and some showed HL The findings, nonetheless, suggest a relationship between the prolymphocytic leukemia of Galton et al. and cases with ++ and +++ in the peripheral blood in my series. Those patients who died in the series of Galton et al had survived on the average 12 months. The patients in my series survived on the average 30 months, while the + cases survived on the average 49 months. Here too comparisons are unreliable It is not possible to gather from the report of Galton et al whether all the patients died from the disease and therefore all the patients in my series were included in the above calculation irrespective of the cause of death but if only those patients who had died from the disease were included the difference would nevertheless be similar 30 (8 cases) against 53 (17 cases) months The cases of Galton et al. had very high WBC, like those of my series with a high percentage of immature cells.

The difference between the series of Galton et al. and mine may perhaps be due to a difference in selection. My group ++ was admittedly very broad but the quality of the smears did not permit any precise grading of the number of immature cells. The cases of Galton et al. consisted, according to the description, of cases with a majority of immature cells but the authors wrote that all the cases had a varying percentage of small lymphocytes, too The comparison between these 2 series may therefore be justified

These findings placed in relation to those mentioned earlier in group 2 in the bone marrow series would thus suggest that the aggressiveness of the disease was better correlated with a high percentage of immature cells in the peripheral blood than in the bone marrow and lymph nodes. One might speculate that this was due to the blood picture being more representative of the situation in the organism as a whole than single bone marrow or lymph node specimens which represent very small volumes of tissue while the blood picture might so to say be the synthesis of the entire lymphatic system This would, however mean an oversimplification because LLD-2 with widespread disease may be aleukemic

I feel that prolymphocytic leukemia and LLD-2 are the same process but possibly that the hematologic picture of prolymphocytic leukemia may occur also in the picture of the lymph node of LLD-1 with large IF Further I feel that LLD-1/CLL and LLD-2/prolymphocytic leukemia are variants of one and the same disease Are these variants, then from the beginning constant in type or is the relation between them comparable to that between chronic myeloid leukemia and terminal myeloblastic leukemia? I cannot give any clearcut answer to this question. The shorter survival of LLD-2/prolymphocytic leukemia might suggest that it is the final phase of LLD-1/CLL. On the other hand there are cases like 671/66 which showed a picture of aleukemic LLD-2 already 148 months before death. It is not probable that this patient had previously had CLL Clinically CLL does not seem to change in character and develop into a hematologically more malignant final phase except in rare cases (it is most often a question of HL when the patient clinically deteriorates rapidly in the end phase) On the other hand during the late phase of the

disease the patient s blood and bone marrow may be examined less often and at any rate prolymphocytic leukemia is uncommon compared with classical CLL. The few cases of "blastic transformation" of CLL reported presumably represent transition to prolymphocytic leukemia One might suspect that prolymphocytic leukemia (like myeloblastic leukemia) may occur both as a primary disease and as the final stage of chronic leukemia. The transition of CLL to HL must be much more common than this development however

4 IF IN NECROPSY SPECIMENS As previously pointed out necropsy specimens are not always satisfactory for classification of diffuse lymphomas because of shrinkage of the cells and autolysis. It is sometimes impossible to find clear-cut IF in necropsy specimens even if such has been found in biopsy specimens of lymph nodes from the same site. This might be because IF are inconstant and disappear in successfully treated patients or for some other reason. But much argues against this possibility In good specimens obtained soon after death and properly fixed it is usually possible to detect IF Further as pointed out above IF do not disappear even after irradiation of the node or successful cytostatic therapy Every pathologist knows that it may be difficult to demonstrate germinal centers in necropsy specimens of normal lymph nodes. The situation regarding IF may be analogous In all the cases judged as LLD-1 in the necropsy material suspect IF could be found somewhere in the tissues examined but they generally had to be searched for and were not easily discerned in most cases, nor were they possible to find in all the tissue blocks examined. However striking IF-like formations were sometimes seen also in technically unsatisfactory necropsy specimens (figs. 112 113). This was because they contained large and atypical cells, which were strikingly different from other lymphocytes even in poorly preserved tissues (fig. 114) Only one of the lymph node biopsies contained such atypical cells in the IF and this was a case where HL was also found in the same node (fig. 147)

The necropsy specimens of the 94 LLD-1 cases were studied in the following way IF-necropsy (IF-n) all cases where the above described foci with atypical cells were demonstrated but without HL 24 cases
HL microscopically clearcut HL 12 cases.
It is apparent from the preceding sections that HL-changes may develop in patients with lymphocytic lymphoma. Also changes resembling those in Hodgkin s disease can develop For the sake of brevity in what follows lesions of the latter type are unless otherwise stated to be regarded as included in the scope of the term HL, because these changes appear to develop in an analogous way

Two of the specimens with IF-n showed suspect HL within IF-n but without really convincing HL One of the HL-cases had only microscopic lesions without any distinct gross difference from other nodes in the case. The other HL-cases had tumorous lesions differing markedly macroscopically from other lesions. The groups thus showed transitional forms.

IF-n. These foci were never seen in all affected tissues of a case. This may perhaps be due to technical factors such as a varying degree of autolysis, but there is no reason to assume that retroperitoneal lymph nodes, for example should have undergone less autolysis than inguinal lymph nodes and the frequency of IF-n differed markedly

before death. The method of electrophoresis had been modified during the study period by replacing paper by agarose The increased sensitivity of the diagnosis of M-components thereby obtained may be the cause of the change in only one case. In the patient where the M-component appeared 12 months before death its con centration was doubled successively until just before death. The remainder had been examined only once or twice so that the tendency was difficult to judge One of the two patients who had his M-component initially was not further controlled,in another the concentration remained unchanged during the rest of life 28 months. The appearance of an M-component in a CLL patient may be an omen malum quo ad vitam and may be a sign that HL is under way

Chapter 9

MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE IN CHRONIC LYMPHATIC LEUKEMIA AND OTHER DIFFUSE LYMPHOCYTIC MALIGNANT LYMPHOMAS

Necropsy revealed Hodgkin s disease in 2 cases and HL in 10 of the LLD-1 series. Unless otherwise stated the 12 cases are treated together below

Of the 2 subjects with Hodgkin s disease one was a 77-year old man and one a 67 year old woman. Of the 10 HL-cases, 7 were men and 3 were women aged 50 82 years at death (mean 71 years)

One of the patients (136/58) had died from complications of myelomatosis 21 months after the diagnosis of CLL the others, from the lymphoma 15 180 months after the diagnosis of CLL (average 60 months)

In 2 of the subjects HL had been diagnosed <u>*intra vitam*</u> *4 months and 15 months*, respectively before death. The latter had sought medical advice because of a nasal polyp which at biopsy was found to be HL, but he was leukemic at that time In the others CLL had been diagnosed long before the appearance of symptoms of HL. The time of onset of the HL-changes was naturally uncertain. In 669/73 a gingival tumour suddently appeared. It proved to be HL and he died within 4 months from widespread HL. 136/58 was examined with lymph node biopsy 8 months before death and then had LLD-1 with IF +++ At necropsy he had only HL in the same lymph node site which had thus presumably developed in the meantime In the other cases no morphologic data were available to date the onset but HL had probably started from 1 12 months before death. They were characterised by very rapid general deterioration. All except 83/64 (HL in stomach) had bouts of fever for several months before death. At least 2 patients had continuous subfebrility interrupted by spells of high fever without evident cause. All complained of extreme tiredness The organ involved by HL at necropsy had grown rapidly in all the cases where examinations thereof had been recorded.

In 83/64 who had gastric HL, the clinical picture was interpreted as rapidly growing *gastric carcinoma The exact time of onset of the symptoms was uncertain but* it was probably much less than 1 year before death.

In 831/70 the initial symptom was swallowing difficulties, and oesophageal carcinoma was suspected. In a few months a large tumour grew through the sternum and ulcerated up through the skin and the patient died about 6 months after the onset of symptoms.

The cases with Hodgkin s disease showed a similar terminal course About 1 year before death general deterioration rapidly appeared with fatigue sweating and spells of fever in retrospect characteristic of Hodgkin s disease Both showed a rapidly growing liver and spleen with pain especially over the liver Both had the most widespread changes of Hodgkin s disease in the liver or spleen.

All 12 patients were leukemic at the time of the diagnosis of CLL, WBC ranging between 11 000 and 211 000 All had on some occasion more than 20 000 WBC. Biopsy specimens had been obtained of the lymph nodes of 4 cases. IF were graded in these in the following way (figures in brackets denote number of months between first biopsy of lymph nodes and death) 1 case + (57 months)

1 case	+	(57 months)
1 case	++	(70 months)
2 cases	+++	(19 and 12 months)

One of the +++ cases had been biopsied again 8 months before death. The findings were the same as on the previous occasion.

The bone marrow had been examined in 9 cases The amount of immature cells in the bone marrow smears was graded as follows

7 cases + (8 14 20 35 40 47 and 109 months)

2 cases ++ (24 and 48 months)

One had ++ in the blood the remainder +

The percentage of immature cells in the bone marrow did not appear to be directly related to the subsequent development of HL, which appears reasonable because of the relatively unusual occurrence of HL in this organ. The 2 cases with IF +++ in the lymph node biopsy developed HL more rapidly than the others, but the number of cases was too small to claim that +++ cases had a greater risk of developing HL.

Six of the patients had received specific treatment before the development of symptoms referable to HL one had received radiotherapy 4 cytostatics, 6 corticosteroids, in various combinations. Five had never received radiotherapy cytostatics or corticosteroids Their average survival time was 35 months (15 48) including the terminal phase Those treated survived including the terminal phase on the average 81 months (30 180) In 1 case the treatment was uncertain because the records were incomplete Thus nothing suggested that the treatment had caused r accelerated the development of HL. The 2 HL-cases diagnosed intra vitam were reated by irradiation of the primary manifestation and with a good local effect but the patients soon died despite treatment (within 4 and 15 months) and necropsy revealed generalisation

There was no characteristic hematologic reaction pattern to treatment of CLL in the cases which eventually developed HL. One showed successively increasing WBC despite therapy one had varying but high values the whole time one unchanged moderately increased values (15 25 000) 3 showed normalisation of WBC after treatment including 2 in whom the values fell to slightly leukopenic levels with absolute lymphopenia and one in whom the WBC later remained normal but with absolute lymphocytosis. In only one (961/61) of these 3 did the WBC remain normal until death the others had recurrences. Of the 5 not treated 4 showed successively increasing values and 1 could not be judged in this respect because the diagnosis of HL had been made at the same time as CLL and the WBC had afterwards fallen during radiotherapy

All the patients except one (961/61 see above) were leukemic just before death It is, of course difficult to date the onset of the HL exactly but most of the patients had deteriorated abruptly in association with growth of the affected organ.

This was followed by a falling tendency of the WBC in 3 no change in 4 a tendency to rise in 4 and no adequate recording for evaluation in 1 of the cases. Two of the 3 in whom the values tended to fall received radiotherapy Thus, the hematologic findings did not suggest that the HL-cases were different from other CLL-cases. Such an "extinction" of leukemia at the onset of HL described in the literature (see discussion in 73) was rare The only case (961/61) with such a tendency is illustrated in fig. IV

The disapperance of lymphocytosis in this case was probably due to radiotherapy

In all the cases the bone marrow showed a varying degree of lymphocytic infiltration at necropsy All showed also residual leukemic changes in other organs. There was thus no reason to assume that the HL-changes eliminate or replace leukemia. This may possibly take place if the entire lymphatic system including the bone marrow is destroyed by HL, but a patient rarely survives long enough for such destruction to occur

All the patients had been examined with electrophoresis on some occasion. The immunoglobulin values showed the following picture (myeloma case excluded)

	Low	Normal	High
Early	5	4	0
After probable start of HL	8	0	1

The patient with a late high value had not been examined before Three showed M-components.

31/67 was a man, aged 77 at death, who had fallen ill 180 months before death. Electrophoretic examination on 4 occasions during his disease showed low immunoglobulins without M-component. The latest electrophoresis 2 months before death showed a plasma component IgMK 0.30 gram/100 ml with background immunoglobulin unchanged. At necropsy he exhibited characteristic changes of Hodgkin's disease

961/61 was a man aged 66 at death, who had fallen ill 47 months earlier Three electrophoretic examinations during the course of the disease had shown low immunoglobulin levels without M-component. Twelve months before death (beginning symptoms of HL) electrophoresis had revealed an M-component in β 2 (0 31 gram/100 ml) Ten months later the concentration was 0 58 gram/100 ml. The background immunoglobulin was falling Necropsy showed HL.

1298/65 was a woman, aged 50 at death. She fell ill 30 months before death. Electrophoresis showed low immunoglobulin values in the plasma. The urine contained a small Igμ-component which persisted at several later examinations, but was not quantified. The plasma immunoglobulin was slightly falling.

Three of 12 cases thus had an M-component in addition to one with IgG-myeloma. Three had not been examined after onset of HL-symptoms.

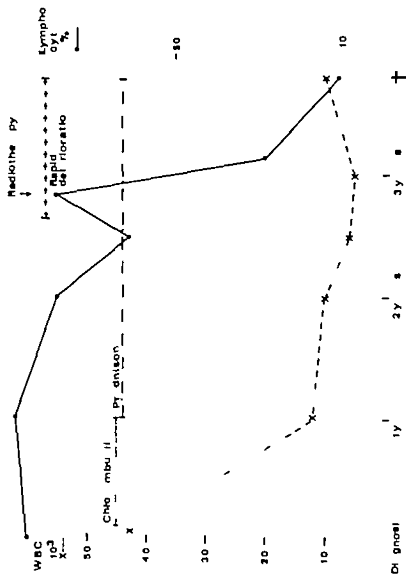


Fig. IV Case history 961/61

TOPOGRAPHY AND PATHOLOGY OF HL LESIONS Symptomatic HL-lesions often appeared in extra-lymphatic sites, especially in the throat and air passages. Eight of the HL-cases (but none of the cases with Hodgkin s disease) had on some occasion extra-lymphatic tumours. 829/69 and 961/61 had a tumour in the para nasal sinuses and the base of the skull as presenting symptoms. 831/70 had a tumour in the anterior mediastinum and 669/73 had a gingival tumour as initial symptom. Four had pulmonary lesions at necropsy which were situated peripherally and did not appear to have originated from peribronchial infiltrates They might however have originated from subpleural infiltrates

The regions of the throat and airways appeared to be responsible for an unproportionally large part of the symptomatic HL lesions also in other groups. 437/67 in group 1 3 also developed HL of the throat and base of the skull. 451/61 (LLD-4) developed HL of the throat and tonsils and 290/70 (LLD-3) of the nasal mucosa.

The changes however sometimes developed first in other organs. 83/64 had a large solitary gastric tumour (fig. 126) but did never develop HL-changes in the lymphatic system In 2 (136/58 and 1434/64) there were never extra lymphatic lesions. All others had not only extra-lymphatic lesions but also HL-changes in the lymphatic system

At necropsy the changes of lymph nodes were situated as follows (HL + Hodgkin s disease)

Supraclavicular	8
Mediastinal	7
Retroperitoneal	6
Axillary	5
Inguinal	2

The higher frequency of changes supradiaphragmatically was probably related to the concentration of the changes in the airways.

The spleen showed changes in 3 cases (weight 850 1370 and 1900 g) Multiple pea-sized lesions were seen macroscopically in all 3 cases.

The liver showed changes in 7 cases (weight 1620 2980 g, mean 1990 g) The smallest liver and spleen had been irradiated because of pain (Hodgkin s disease) and had markedly decreased in size before death. Six of the 7 had grossly visible multiple lesions ranging from a diameter of some millimetres to about 3 x 3 cm. All the lesions in a given case were of roughly equal size All the smaller lesions of HL and Hodgkin s disease were surrounded by lymphatic tissue like IF-n. They often had the same external contour as the lymphatic infiltrate in which they were situated In the largest lesions all pre-existing structures had been destroyed

Only in 3 cases did the bone marrow show HL-changes, always microscopic. 136/58 had widespread osteolytic myeloma infiltration, while the rest of the marrow showed lymphocytic infiltration with single very small HL foci. 1298/65 had small HL foci in the femoral marrow while the vertebral bodies showed a picture similar to that of LLD-2 with fibrosis but without HL. 31/67 exhibited fairly widespread Hodgkin s infiltration of the vertebral bodies but without bone destruction or macroscopic lesions.

The involved lymph nodes were always markedly enlarged and with one exception (38/73) had a sarcomatous appearance with confluent aggregates with grey white cut surfaces and often necroses. In 38/73 the picture of the lymph nodes involved differed only little from that of the others in the case except that they were larger In this case the changes had partly the character of HL in IF-n. The patient had however also tumorous HL in the lungs. In 6 there were areas with a picture of LLD-1 with IF-n in other parts None had HL in all lymph node sites. In the necropsy specimens the HL-involved lymph nodes were nearly entirely affected probably because the pathologist had selected large nodes for microscopy Biopsy of 829/69 showed a pea-sized HL focus in an otherwise lymphocytic node (fig 152) The HL-focus was fairly well demarcated but surrounded by coalescent IF (fig. 146)

In 4 cases the clinical symptoms at the onset of HL suggested a solitary extra lymphatic tumour Presumably it is rarely a question of such a tumour however The short survival time despite successful local treatment combined with widespread lesions at necropsy suggest that the process had been widespread already before HL had been diagnosed. Especially the picture of the liver lesions suggested multiple simultaneous origin from IF-n in this organ It seems probable that a transformation into HL can occur systemically but that lesions in the throat are most apt to produce early symptoms Cytostatic therapy rather than local radiotherapy might possibly have retarded the course or offered palliation On the other hand there were cases with solitary lesions and in such cases radiotherapy is indicated in spite of the risk that similar changes soon may develop elsewhere The most important sites of IF-n and HL seemed to be the central lymph nodes and liver The changes were seen less often in the peripheral nodes and spleen and it is remarkable that the bone marrow was not involved more often Gross or destructive lesions were never seen in the bone marrow and microscopically only very small changes except in 31/67 with Hodgkin s disease The bone marrow is the least rewarding organ to examine in suspect transformation Rapidly growing organs should of course be examined first lymph nodes, liver or spleen. Fine needle aspiration biopsy is probably sufficient to obtain a provisional or firm diagnosis of transformation

Clear HL (+ Hodgkin s) changes developed in 12 of 94 (about 13 %) It is clear from what was said above that it is reasonable to assume that all cases with IF-n were really "pre HL and if so 36 of 94 in the series would thus have HL or pre-HL" at necropsy i e about 38 % It might be of interest systematically to examine CLL-cases which appear to be in the terminal phase with respect to electrophoresis immunological status etc The possibility of obtaining cells for morphologic and cytochemical studies by fine needle aspiration biopsy should also be considered

HISTOLOGY OF HL LESIONS The 2 cases of HODGKIN 'S DISEASE will be considered first

31/67 showed widespread changes in the lymph nodes. The liver contained both large and small and sometimes coalescent lymphatic infiltrates in the portal tracts. The larger infiltrates showed lesions characteristic of Hodgkin s disease (fig 116) They were always surrounded by a brim of lymphocytic tissue which had the same outer contour as the foci of Hodgkin s disease in the center (fig. 115) The largest

lymphocytic infiltrates had several small foci of Hodgkin s disease often symmetrically situated and always with a preserved lymphocytic margin The foci of Hodgkin s disease showed characteristic Reed Sternberg cells, macrophages (fig. 117) plasma cells, eosinophilic leukocytes and fibroblasts as well as fibrosis and small necroses. The changes had partly a granulomatous appearance and were clearly Hodgkin s disease of mixed cellularity type The changes in the lymph nodes were generally of the same appearance but partly of lymphocyte depletion type as in the bone marrow The surrounding bone marrow showed a picture of CLL like some of the lymph nodes.

692/66 showed changes of Hodgkin s type only in the liver and spleen, while lymph nodes and bone marrow showed a picture of CLL. Lymph nodes and liver showed prominent IF n The spleen (1370 g) contained abundant grey-white foci the size of a pea which macroscopically were well outlined against the surrounding splenic parenchyma They were microscopically built up of mainly prolymphocytes. Among them there were smaller foci of histiocytes with phagocytosis of erythrocytes and lymphocytes, and Reed Sternberg cells (fig. 118) but no plasma cells or eosinophilic leukocytes and no fibrosis. The changes in the liver were of the same type (fig 119) Also these changes were grossly tumorous and grey-white The diagnosis of Hodgkin s disease was thus based here on the Reed Sternberg cells and histiocytes, but the environment was not typical of Reed-Sternberg cells.

THE 10 CASES OF HL PROPER differed from one another in appearance In 38/73 the lymph nodes showed no gross signs of HL, but microscopically all lymph node sites except those in the groins exhibited large coalescent IF-like foci with pictures which in large parts must be interpreted as HL and pulmonary HL-foci 1 cm or more across The lymph nodes contained transitional forms between IF 1 cells and HL-cells with abundant cytoplasm and large nucleoli. The picture resembled that of "immunoblastic sarcoma (47)

Most of the cases in the series had areas of this type Besides the above mentioned case there were 6 of mainly this appearance but with considerable individual differences 83/64 (gastric) showed considerable variation in cell size and the cytoplasm was often sparse 1434/64 (fig. 134) 1 98 65 (figs. 121 1_5) 879/69 (figs. 152 160) 831/70 (figs 1_7 1 8) and 669/73 (figs 144 145) were similar in that they all had mainly round cells of roughly uniform size but a number of very irregular nuclei and cells with long processes were always seen and always a small percentage of lymphocytes among the tumour cells. The nucleus always showed a certain condensation of the chromatin often peripherally in a way resembling what is seen in IF-cells but sometimes of coarser and irregular type which gave the nucleus a plasmocytic appearance (fig. 154) Large nucleoli were often seen, but not always. Mitotic figures were numerous in all the tumours in the HL-group A large percentage of dying or dead cells were always seen in the tumours, often phagocytosed in histiocytes (figs 155 156) Phagocytosis was always seen in these tumours yet it was generally easy to see that this was not in neoplastic cells. The lung tumours never contained carbon pigment in HL-cells, but they did in reactive histiocytes.

Three cases were of more special type

Case 47/65 had tumours in the liver with lymphocytic predominance but with

abundant very large atypical cells, often with several nuclei and giant nucleoli and the picture showed considerable similarity to the changes seen in Hodgkin s disease but typical Reed Sternberg-cells were never seen (fig. 132) The lymph nodes showed unique changes (lung hilus, supraclavicular fossa paraaortic) The parenchyma contained small foci of the "immunoblastic sarcoma-type described earlier (fig. 130) They broke out into the lymph node sinus and the cells spread along and within the sinus (figs 129 131) The cellular picture was polymorphous and of "histiocytic" appearance Many cells appeared to be atypical, fibril-associated sinus endothelium, others free sinus histiocytes but all atypical, sometimes bizarre Many of the cells in the sinus contained lymphocytes The lymphocytes were sometimes degenerated but often they appeared to be vital and the cytoplasm of the large cells contained suspect lymphocytic mitotic figures. One might consider the possibility that the included cells represented a form of emperipolesis, rather than phagocytosis

This patient also had pulmonary lesions. In one area alveolar septa and interstitium showed dense lymphocytic infiltration (fig. 133) These infiltrates contained many atypical cells of the same appearance as in the liver Such atypical cells were abundant in the alveoli (in this area not elsewhere in the lungs) together with obvious alveolar macrophages with erythrophagocytosis. This patient had not received radiotherapy or cytotoxic substances. The alveolar macrophages may sometimes be very atypical after treatment but here the cells were obviously identical with those in the lymphocyte infiltrates. Mitotic figures were seen also among cells in the alveoli The changes in this case would probably have been regarded by most pathologists as malignant histiocytosis or histiocytic medullary reticulosis. One could however see morphologic transitional forms between the immunoblast-like and the histiocyte-like cells.

In 136/58 the lymph nodes liver and spleen showed a very bizarre proliferation in the form of large tumorous nodules The cells were similar to those in the preceding case (fig. 135) They showed complex tortuosity of the nuclei and abundant cytoplasm with vacuoles and often spider like inclusions in vacuoles Between these cells there were very large amounts of histiocytes with obvious phagocytosis of both erythrocytes and lymphocytes. Both types of cells showed mitosis and the cytoplasm was of similar appearance But no bizarre cells with obvious phagocytosis were seen. Some lymph nodes and other lymphatic infiltrates showed an ordinary CLL-picture without histiocytic infiltration and it was obvious that the bizarre cells and the phagocytising histiocytes were topographically related to each other The treatment of this patient is unknown because his hospital records were incomplete It might be added that HL-tissue was everywhere related to the lymphatic infiltrates never with myeloma foci which the patient had in the skeleton Also this case would probably have been regarded by most pathologists as malignant histiocytosis or histiocytic medullary reticulosis.

In 961/61 the patient had HL-changes in the lymph nodes, paranasal sinuses and base of the skull. In this case the tumour was clearly fibroplastic (figs 138 139) The tumour-cells were very polymorphous and grew fascicularly in some areas almost like fibrosarcoma with abundant reticulin and collagen between the tumour

cells (figs 140 141) Between these fascicles of connective tissue-like tumour cells were free cells, also anaplastic and with vacuolated cytoplasma but without phagocytosis and cells with plasmocytoid features (fig. 142) This patient had received short terminal radiotherapy of the cervical lymph nodes, but also non-irradiated lymph node sites showed the same picture These changes would presumably have been regarded by most pathologists as malignant histiocytosis or possibly even malignant fibrous histiocytoma

HL-CHANGES IN OTHER GROUPS The HL-changes are summarised in table 15

	Total number in series	Developed HL	%	
LLD-1	94	12	13	12
LLD-2/Bone marrow group 2	12	1	8	
Bone marrow group 1 3	4	1	25	
LLD-3	9	5	56	
LLD-4	15	1	7	
LLN	13	6	46	
Macroglobulinemia *	9	2	22	

incl non-Malmö-cases

Table 15 HL in lymphocytic lymphomas in total material.

The bone marrow group 2-case with HL was 655/63 The patient a man aged 81 at death, had sought advice because of generalised enlargement of the lymph nodes which he had had for 2 years. The liver and the spleen were moderately enlarged WBC 43,500 with 98 % lymphocytic cells and immature ++ He had some very large atypical cells with several nucleoli and irregular nuclei (fig. 164) The bone marrow contained 50 % lymphocytic cells with immature +++ (fig. 163) Electrophoresis showed immunoglobulin 0 48 gram/100 ml and a monoclonal component of 0 60 gram/100 ml of IgM-type The urine contained an Igμ-component. The patient was treated with chlorambucil which was withdrawn after 12 days because of nausea and was replaced by corticosteroids He survived 14 months and was troubled by intermittent attacks of fever WBC varied between 13 000 and 92,000 without any clear tendency The hemoglobin concentration fell successively the concentration

of the monoclonal component remained unchanged

Necropsy showed diffuse myelofibrosis with lymphoid infiltration (fig. 165) The spleen was shrunken after a subtotal infarction the liver was of normal size but showed fibrosing lymphatic infiltrates in the portal tracts. The lymph nodes were enlarged and showed stratified fibrous foci, where the periphery sometimes consisted of polymorphous plasma cell-like forms A markedly enlarged axillary lymph node showed a central multi lobulated HL focus (fig 167) It was made up of a mixture of IF-cells, small lymphocytes and bizarre multinucleated cells, in some respects resembling Reed Sternberg cells. They had very basophilic cytoplasm No fibrosis in this focus (figs. 166 168 170)

The stratified hyaline foci in the lymph nodes might perhaps have been "healed" HL of the same type as the highly cellular lesions in the axillary lymph node It should be observed that the patient had not received radiotherapy or aggressive cytostatic therapy which might have resulted in extensive tissue destruction. Both clinically and morphologically the condition resembled Hodgkin s disease but the cells fitted in best with the group "pleomorphic HL" (see 55)

Group 1 3 (see chapter 5) One of the 4 patients in this group developed HL (437/67) The leukemia had been diagnosed in this man 246 months before death, but he had had hardly any symptoms and received no treatment for about 20 years. Seven months before death he began to have swallowing difficulties because of a tumour of the mesopharynx Biopsy showed HL in the form of densely packed large round cells with prominent nucleoli (fig 75) The cells contained PAS-positive hyaline inclusions. Such inclusions were seen as Russel-body-like structures in smears from the cervical lymph nodes where the cells were very polymorphous with complex tortuosity of the nuclear contour (fig 74) The WBC at the time of diagnosis of HL was 175 000 Deltisone and radiotherapy were given but the patient died from increased intracranial pressure Necropsy showed a large tumour of the throat which had broken through the base of the skull and into the cerebellum HL was found also in the cervical lymph nodes and in the supraclavicular fossa as well as in the retroperitoneum. The bone marrow and liver showed lymphocytic infiltration without HL as did other lymph nodes The spleen showed clear IF suggesting that in this case the picture of a biopsy specimen might have been of type LLD-I despite the atypical cytology In some areas, the tumour cells closely resembled plasma cells and were full of Russel-body like formations which pushed the nucleus to the periphery (fig. 79) The lymphocytes never contained such inclusions

This patient had an M-component (IgGK) already at the first electrophoretic examination about 5 years before death. Repeated control examination showed unchanged concentration (0 30 0 40 gram/100 ml)

A further patient (913/7_) in this group had an M-component It was observed at the first examination 30 months before death It had increased slightly in concentration by the time of the last examination 1 month before death. The patient died from myocardial infarction 49 months after the diagnosis without having had any noteworthy symptoms of th leukemia The necropsy specimen contained some lymph nodes with undoubted IF

LLD-3 Of the 9 patients 5 developed HL.

1120/60 survived only 7 months after the diagnosis At the time of the diagnosis the WBC was 6,200 with 68 % lymphocytes with occasional atypical ones (fig. 36) The bone marrow showed moderately dense diffuse infiltration of partly atypical lymphocytes without evident immaturity (fig. 35) thus a picture best compatible with LLD-3 This patient was given radiotherapy towards the peripheral nodes, which were generally enlarged The WBC increased but did not reach leukemic levels, but the percentage of lymphocytes exceeded 90 Afterwards the WBC fell as did the percentage of lymphocytes after treatment with chlorambucil. During the last 2 months the patient became rapidly worse with frequent fever peaks and intractable growth of the lymph nodes. At the time of diagnosis the biopsy specimen of the lymph node showed LLD-3 (fig. 37) At necropsy HL lesions were predominant in the lymph nodes of the mediastinum and retroperitoneum (fig 38) while peripheral lymph nodes showed LLD-3 The bone marrow exhibited the same picture as at the time of the diagnosis (fig. 34)

This patient had an M-component (IgGL) which increased in concentration during 6 months in the following way 0 57 0 97 1 04 1 41 gram/100 ml

855/67 a man aged 63 at death survived 137 months after the diagnosis. He had then already a history of many years with enlargement of the peripheral lymph nodes chills, diarrhoea splenomegaly and purpura of hyperglobulinemic type Liver biopsy 5 years before the diagnosis showed portal lymphocytic infiltration (specimen no longer available) He had a positive test for antinuclear factors and a massive diffuse increase in immunoglobulins, 5 6 gram/100 ml. Examination of the bone marrow on 8 occasions during the disease showed massive plasmocytosis but never lymphoma infiltrates. Never were the blood values leukemic but occasionally there were up to 60 % "atypical lymphocytes in the peripheral blood Autoimmune disease was suspected The diagnosis of lymphoma was obtained at exstirpation of the spleen and biopsy of a retroperitoneal lymph node Splenectomy improved the strange clinical picture and for some years after a short course of TEM-treatment the patient felt much better After 3 years the patient s general condition became worse again and severe anemia developed He was given chlorambucil and improved considerably Six years before death an M-component of IgM-type appeared It reached a concentration of 2.45 gram/100 ml. Corticosteroid treatment was started and the patient improved clinically and the M-component disappeared He began to drink heavily however and deteriorated rapidly During the last 6 months of life the patient had continuous fever alternating with temperature peaks of above 40°C with severe chills. Massive neutrophilia 30 40,000 WBC The patient died in a state of shock.

Necropsy showed intestinal bleeding. The liver was cirrhotic. The liver and retroperitoneal lymph nodes showed HL (figs. 173 174) and the HL-tissue necrotising arteritis and massive granulocyte infiltration (fig. 175) HL was of characteristic immunoblastic type. HL-foci were always surrounded by lymphocytic infiltrates

290/70 a woman aged 84 at death had as a first symptom of her disease bleeding from a polypous HL in the nose (fig. 177) The enlarged cervical lymph nodes were punctured and showed a dominance of large round tumour cells with very

basophilic abundant cytoplasm and often excentric nuclei (fig 178) Other palpable lymph node sites contained only nodes of normal size but the liver and the spleen were considerably enlarged The WBC and percentage of lymphocytes were normal Marked polyclonal increase of immunoglobulins No M-component The patient was treated with irradiation of the neck and was in a good condition for some time but later had gastrointestinal bleeding which proved fatal 8 months after the diagnosis. Never lymphocytosis of the blood Necropsy showed HL of the lymph nodes in the supraclavicular fossa and retroperitoneum as well as an ulcerated tumour in the stomach which was the origin of the fatal haemorrhage Centrally the tumour showed HL and in the periphery LL Other lymph node sites showed LLD-3 as did the liver spleen and bone marrow (fig. 176)

This patient had probably had asymptomatic LLD-3 for some time The enlargement of the spleen and liver found already at the time of the diagnosis was due as judged from the necropsy findings to LLD and not to HL. The symptoms however did not appear before HL-transformation in the air passages. Literature cases of CLL appearing after HL (see 73) are probably cases of this type where HL developed from aleukemic LLD-3 and where the lymphocytic part did not become leukemic until after HL transformation If the primary HL-manifestations are successfully treated LLD may persist and give rise to a leukemic blood picture later

705/70 was a man aged 63 at death Lymphoma was diagnosed 27 months before death but he had a previous 5-year history of asymptomatic enlargement of the cervical lymph nodes. WBC at the time of diagnosis 4 000 72 % lymphocytes. The patient was treated with Prednisone and chlorambucil and the WBC fell, first to subnormal level afterwards it rose again and reached 13 700 with 97 % lymphocytes. Four months before death the patient deteriorated rapidly with anemia loss of body weight and shortness of breath as well as constant fever Roentgen examination showed a rapidly growing mediastinal tumour Electrophoresis of the urine showed an M-component in the form of kappa-chains in low concentration This examination had not been done before The serum immunoglobulin had fallen to normal level after previously having been increased The patient died from hyperpyrexia

Necropsy showed HL in the mandarine-sized mediastinal lymphomas LLD in other lymph nodes, liver spleen and bone marrow HL was histologically of immunoblastic type

1140/71 was a 58 year old woman who survived for only 7 months after the diagnosis From the beginning she had generalised enlargement of the lymph nodes. WBC 4 600 lymphocytes 42 % slight bone marrow infiltration (fig 29) The lymph nodes showed many immature cells similar to IF-cells but more irregular in shape and size They were somewhat unevenly distributed in loose collections which could have some slight similarity to IF In spite of treatment with Velbe and irradiation the patient deteriorated very rapidly Post mortem revealed in most sites diffuse lymphocytic lymphoma The mediastinal supraclavicular and retroperitoneal nodes, and the liver and spleen contained foci of a bizarre-celled tumour most closely resembling Hodgkin s disease (figs 31 32) The foci had a slightly granulomatous appearance and contained many multinucleated cells resembling

Reed-Sternberg cells. Plasma cells and eosinophilic leukocytes were sparse

In LLD-3 then 5 of 9 developed HL or Hodgkin s disease. Three of those 5 had monoclonal immunoglobulin components Another patient (220/72) in this group also had a small monoclonal component in the form of light chains in the urine This patient died from non-lymphoma disease 40 months after the diagnosis, 15 months after the detection of the monoclonal component.

LLD-4 One patient in this group (451/61) developed HL. This patient had both clinically and microscopically some similarities to LLD-3

451/61 was a man aged 60 at death who had had leukemic disease for 27 months. He had constantly had diffusely increased immunoglobulin without M component He was treated from the beginning with chlorambucil and Deltisone The spleen caused mechanical symptoms and hyperhemolysis and was removed 1 year after the diagnosis. It weighed 2 800 g and showed massive lymphatic infiltration of the red pulp and expanded follicles with cells of LLD-4-type The lymph nodes in the spleen hilus exhibited massive plasma cell infiltration in the tumour tissue (but the spleen did not) The increased immunoglobulin level was not affected by splenectomy but the hyperhemolysis disappeared The patient was afterwards in a good condition until 4 months before death, when the liver and the lymph nodes increased rapidly in size and the patient died after rapid deterioration despite irradiation of several lymph node sites. Terminally the WBC was about 40 000 with no tendency to fall or rise

Necropsy showed HL in all the lymph nodes, tonsils, liver retroperitoneal soft tissues etc. There was insignificant residual lymphatic infiltration except in the bone marrow where HL was seen as small foci in diffuse lymphocytic infiltrates. The liver (3 400 g) showed a picture that could not be distinguished from that of the corresponding changes in the CLL-cases, a portal lymphocytic infiltration with central foci of HL. HL was histologically of the immunoblastic type with large round cells with abundant cytoplasm and prominent nucleoli, but with coarse chromatin structure

LLN Almost 50 % of the patients in this group developed HL (figs 179 180) These cases will not be further dwelt upon here As a general rule it can be said that the HL-tissue in these cases was more polymorphous than in the above-mentioned groups. In most of the cases extra-lymphatic HL-tumours were found in many sites.

RELATION HL MONOCLONAL IMMUNOGLOBULIN COMPONENTS The monoclonal immunoglobulin components in some of the groups and their relation to HL are given in table 16 In LLD-4 and LLN only 1 patient with monoclonal immunoglobulin component was seen in each group and the figures are not included for those types. In the groups included in table 16 45 % of the patients with monoclonal components developed HL, compared with 12 % of those without monoclonal component i.e. HL was more than 3 times as common in patients with a monoclonal component.

If IF-n be regarded as potentially HL, it will mean that all together 78 % of the patients with monoclonal components in the material developed HL or potential HL (14/18) Further it should be observed that the monoclonal components

Diagnosis	Number of patients examined with electrophoresis	With monoclonal immunoglobulin components			Without monoclonal immunoglobulin components	
		Number	HL	IF n	HL	IF n
LLD-1	77*	11	3/11	6/11	9/66	18/66
LLD-2/Group ?	11	1	1/1		0/10	
LLD-3	8	4	3/4		1/4	
Group 1 3	4	2	1/2		0/2	
Total	100	18	8/18		10/82	

One excluded because of myeloma with monoclonal component This patient also developed HL

Table 16 Relation between monoclonal immunoglobulin components and HL in some lymphoma group

appeared to occur most often late in the course of the disease. In many of the HL cases there was no electrophoretic control examination during the last year (as, of course in the other cases) In about 25 % of the cases with HL or IF n but without known monoclonal component no electrophoresis was performed during the last year of life

The findings lend strong support to the assumption that HL is a neoplasm of the immunoglobulin producing cell series, at any rate the HL that develops in the final phase of the above-mentioned groups of lymphocytic lymphoma. It has not been proved by these observations that the monoclonal components really are produced by the tumour cells, but they probably are

Chapter 10

SPECIAL HISTOLOGIC AND ELECTRON MICROSCOPIC STUDIES

It has been claimed (37) that positive staining with periodic acid Schiff (PAS) in lymphocytic tumour cells excludes the diagnosis CLL, even if it is only a question of an occasional cell. The PAS-positivity may be diffuse in the cytoplasm or it may be seen as globules in the cytoplasm resembling Russel bodies in plasma cells (fig 161) Also it may be seen as globular nuclear inclusions (fig 162) resembling so-called Dutcher bodies in macroglobulinemia (see chapter 1) Such PAS-positivity is said to be a sign of production or storage of immunoglobulins, which, according to Lennert et al. (37) excludes the diagnosis CLL by definition This is obviously a semantic question I will return to this point in chapter 12

All the lymph node biopsy specimens from groups LLD-1 2 and 3 from which tissue was available were stained with PAS The results are given in table 17 and compared to the immunoglobulin recordings of the case

PAS-positivity of the above mentioned types does not appear to have any close connection to monoclonal immunoglobulin components in plasma This does not exclude that the PAS-positivity represents storage of immunoglobulins intracellularly but this aspect was not studied in the present material.

The PAS-positive cells were not numerous in any case of LLD 1 The classification as positive or negative was made after search in one section but case 258/68 (registered as positive in table 17) was negative in the first section In order to check the reliability of a classification based on PAS-staining 5 sections were made of this case and searched in oil immersion magnification In the 3rd section one cell with a typical intranuclear globule was found (fig. 162) and one cell with typical intracytoplasmatic globules (fig. 161) It is thus evident that a vast amount of cells may have to be examined before a positive example is found. When should a specimen be declared as negative? It appears little useful to attempt a *histologic* classification based on this single criterion Also similar hyaline globules staining negatively with PAS may be seen in LLD-1 (personal observations) PAS-staining is not always reliable when performed on necropsy specimens. It was therefore not judged as useful to perform the reaction on all the necropsy cases.

Representative tissue from all of the above mentioned HL-cases in the groups LLD-1 LLD-2/bone marrow group 2 bone marrow group 1 3 and LLD-3 were stained with the methods described below When biopsy specimens were available they were used otherwise necropsy specimens In one case with IF-n a node was also stained and biopsy nodes of the 2 cases of LLD-2 Further the spleen with HL from the macroglobulinemia case 1?_4/70 was stained

Giemsa
Silver impregnation for reticulin
Per iodic acid Schiff (PAS)
Pyronin and methyl green

DIAGNOSIS NUMBER OF CASES WITH MATERIAL AVAILABLE FOR PAS STAINING	PAS POSITIVE LYMPHOCYTIC CELLS PRESENT	PAS POSITIVE CELLS WITHOUT MONOCLONAL IMMUNOGLOBULIN COMPONENT	MONOCLONAL IMMUNOGLOBULIN COMPONENTS WITH PAS POSITIVE CELLS	MONOCLONAL IMMUNOGLOBULIN COMPONENTS WITHOUT PAS POSITIVE CELLS
LLD-1 12	5	3	2[x]	1
LLD 2 2	0			
LLD-3 7	3	1[xx]	2	

[x] ONE OF THE PATIENTS HAD MYELOMA

[xx] THIS PATIENT DEVELOPED A MONOCLONAL COMPONENT 5 YEARS LATER

Table 17 Relation of PAS-positive cells and monoclonal immunoglobulin components.

Prussian blue
van Gieson
Ladewig
Naphthol-AS-D chloracetate esterase

The last mentioned staining method was done according to (34) Ladewig according to (32) All others, according to the routine methods of the laboratory

This part of the investigation was not very rewarding.

GIEMSA Staining of necropsy specimens is unreliable In the biopsy specimens, IF 1-cells can be shown to have intensely basophilic cytoplasm and darkly staining nucleoli (fig 182) IF 2-cells have a greyish staining of the cytoplasm and nucleoli (fig 182) The biopsy specimens with HL showed a very variable basophilia of the tumour cells in the individual cases but a large percentage was always very basophilic Examination of smears with May-Grünwald-Giemsa staining is preferable if the different cell types can be identified in the specimens for cytological study

Giemsa-stained sections were used for an evaluation of mast cells. Such cells were not estimated to be more numerous in cases with monoclonal immunoglobulin components than in other cases.

PYRONIN AND METHYL GREEN Also this stain is less reliable when performed on necropsy specimens, at least when the tissue has been fixed in formalin The pyroninophilia was parallel with basophilia in Giemsa and the staining is not very meaningful

NAPHTHOL ASD-CHLORACETATE ESTERASE Mast cells and polymorphonuclear leukocytes in the sections are practical controls, as they stain positively

The HL-cells were invariably negative This argues strongly against confusion with myeloid leukemia or extra medullary hematopoiesis In the biopsy specimens some reactive histiocytes always showed some slight reaction the tumour cells, never IF-cells and prolymphocytes were always negative

LADEWIG After Lennert s recommendation this staining was done which is said to allow differentiation of immunoglobulin containing inclusions of cells in such a way that IgM-containing inclusions stain blue-grey and IgA or G containing inclusions red Three cases showed hyaline inclusions in abundance in some cells namely the spleen in the macroglobulinemia case (1224/70) where the inclusions stained red and 437/67 (monoclonal component of IgG-type) where the inclusions stained red in some cells, blue in others and in still others both red and blue (fig 80) This varying stainability was not affected by variation in the technique by changing the staining times or concentration of the stains. Case 31/67 (monoclonal component of IgM-type) had numerous plasma cells with PAS-positive inclusions in the foci of Hodgkin s disease They stained bluish in Ladewig The result was thus not in agreement with what was expected and is not discussed further

PRUSSIAN BLUE Practically all tissues contained some stainable iron in reactive histiocytes. The spleen in the case of macroglobulinemia contained abundant iron but never in the tumour cells Nor was stainable iron found in any other case in tumour cells, not even in the apparently histiocytic cells in 42/65 961/61 or 136/58 But all of these specimens had been obtained at necropsy

SILVER IMPREGNATION FOR RETICULUM FIBERS IF and IF-n had no characteristic reticulum pattern nor had LLD-2 All the HL-cases showed some reticulum fibers, but characteristic relation to tumour cells in only 2 cases (42/65 and 961/61)

42/65 had abundant reticulum associated with the proliferation of tumour cells in the sinus (fig. 131)

961/61 showed a fascicular growth of tumour where the pattern of the cells was closely followed by a dense fibrillar network with both reticulin and van Gieson-positive collagen (fig. 139)

The HL of case 655/63 (LLD-2) contained abundant reticulin as well as collagen The fibers were coarse and PAS-positive The hyaline foci in 655/63 were strongly PAS-positive (but negative in stains for amyloid)

The HL in 829/69 showed at electron microscopy abundant reticulin-like material (fig 160) which could not be demonstrated light microscopically by silver impregnation

Silver impregnation is often meaningless because the fibers are seen in PAS and when there is much reticulum, the cells have an arrangement showing this already on routine-staining.

PAS Sections of necropsy material stained with PAS should be judged with caution Practically all the cases showed diffuse staining in single reactive histiocytes and also in some tumour cells, especially those that appeared necrobiotic. Three cases showed PAS-positive globules in many cells

1224/70 (macroglobulinemia) The HL in the spleen showed many cells with large hyaline inclusions. In some of them the nucleus had been pushed to the periphery They were strongly PAS-positive (same inclusions as those that stained red in Ladewig)

Biopsy of the throat tumour (HL) in 437/67 showed abundant small PAS-positive globules in many tumour cells (fig. 79) Necropsy specimens showed more advanced changes of this type The globules resembled Russel bodies.

In foci of Hodgkin s disease of case 31/67 there were many cells with the morphology or ordinary plasma cells, which contained densely packed small PAS-positive globules.

In 1224/70 the inclusions were so large as to deform the nucleus and it is therefore difficult to say whether they really were situated in HL-cells. Also surrounding infiltrates showed such globules but fewer than in the HL focus.

The cells with PAS-positive globules in 31/67 had a characteristic plasma cell morphology It is not unusual to find PAS-positive globules in reactive plasma cells in inflammatory conditions. A connection with the tumour proliferation cannot be regarded as proved

437/67 showed Russel body-like formations which were undoubtedly situated within the tumour cells.But this does not definitely prove that the cells are producers of immunoglobulin One can find PAS-positive hyaline inclusions also in reticular cells in benign hyperplasia of the lymph nodes.

These histologic studies are thus non-conclusive in the evaluation of the nature of the cells To locate the site of production of the M-component immuno-histochemical studies would have been preferable The difficulties encountered in fixed material are obvious but can possibly be overcome Investigation of this point are in progress

ELECTRON MICROSCOPY In none of the cases had material been ideally fixed for electron microscopy but some information can be obtained from material fixed in formalin if this fixation has been good All the specimens studied were obtained from paraffin blocks. The tissue specimens were originally fixed in 10 % neutral formalin for a varying length of time They were afterwards prepared for light microscopy according to routine methods and embedded in paraffin. With the light microscopic section as a guide an interesting part of the block was cut out It was deparaffinised in xylene and passed through a series of ethanol dilutions to water and postfixed in 1 % osmium tetroxide in phosphate buffer at pH 7 3 The specimens were dehydrated in a graded ethanol series and treated "en bloc" with 1 % phosphotungstic acid and afterwards passed through styrene to Vestopal Sections (1 μ) were cut and stained with toluidine blue For electron microscopy the ultrathin sections were stained with uranyl acetate and lead citrate Mounting on single-hole formvar film-coated grids was found useful to survey large areas

The description of IF is based on 3 cases one of which is not otherwise included in the present material The patient was a man aged 62 with recently diagnosed CLL WBC 500 000 with immature ++ (also in the bone marrow) but predominantly small and mature lymphocytes. Low immunoglobulin level. No M-component No PAS-positive inclusions The biopsied inguinal lymph node was the size of a walnut and showed IF +++ (fig 181) This specimen was best preserved and unless otherwise stated the illustrations originate from it but the other cases exhibited similar changes The case will be referred to as 2 219 The other two specimens were lymph nodes from 829 /69 and 669/73 which were also examined in HL-phase in respectively biopsy specimens of a lymph node and of the gingiva Further lymph node biopsy specimens from 663/58 and 671/66 (LLD-2) and of the pharynx (HL) of 437/67 (group I-3) were examined

CLL. The larger the lymph node the closer the cells were crowded which is perhaps natural owing to the tight capsule of the lymph node

In all the cases the mature lymphocytes were preponderantly round but occasional nuclei with deep clefts or with crenated contour were always seen Many of the mature lymphocytes contained a small nucleolus, often annular and often adjacent to a mass of condensed chromatin The heterochromatin was mainly peripheral but blocks of heterochromatin were always seen also more centrally within the nucleus. The cytoplasm contained free ribosomes polyribosomes and sometimes single short strands of granular endoplasmic reticulum (GER) as well as mitochondria and a Golgi complex The outline of the cells was most often smooth but interdigitation was sometimes seen.

IF IF were characterised by extremely complex surface relations between the cells which had long interdigitating processes and no free intercellular space was apparent (figs. 183 189) In a single plane of section it was often difficult or im

possible to decide from which cell a given process extended but after tedious examination it was possible to form an opinion of the relation of the organelles of a process to a certain type of nucleus The cell nuclei in IF were sparsely distributed which probably explains why IF appear as pale areas in low magnification in the light microscope This sparseness was due to the large amount of interdigitating processes and the more abundant cytoplasm in the IF cells than in mature lymphocytes in the surroundings. In sections from one single plane it was often impossible to classify every cell electron microscopically because the sections are so thin that they can contain only a limited number of cellular elements The description is based to a certain extent on serial sections and it is difficult to illustrate all the characteristics of the various types of cells in a few reproductions. After exacting work with these structures I felt that all forms of cells in IF are genetically related and that there are at any rate such similarities between them that for the reasons given above it is not possible to classify every single cell in a single plane of section Sometimes cells were seen which appeared to have features intermediate between those of the main types. It cannot be excluded that such intermediate forms of cells really exist and are examples of different developmental stages but it is more likely that the phenomenon was generally due to sectional effects. A tangentially sectioned immature cell may be difficult to distinguish from a mature lymphocyte because a tangential section of the nucleus leaves the impression of greater condensation of the chromatin and because the types of cells resemble each other in cytoplasmic structure. But if the section passed through the nucleolus it was usually possible to classify the cell.

The following main types of cells could be distinguished

1 Mature lymphocytes, which did not differ from those in the surrounding parenchyma

2 Prolymphocytes. The chromatin condensation was not so marked as in the mature lymphocytes and the nucleolus was more prominent and had a more marked nucleolonema The cytoplasmic structures, however were very similar to those of 1 *The prolymphocytes were smoother in outline than the following types of cells,* but single interdigitations were seen along the outline of every cell.

3 IF 1 cells. These cells were uncommon and could be detected only after a search in light microscopic sections, and even then they were sometimes difficult to find. The diameter of the nucleus was 3-4 times that of the nucleus of mature lymphocytes (fig. 188) IF 1 cells were often situated close to a small vessel. The nucleus was never quite round and it had not the smooth outline of the IF 2 cell Several nucleoli without any particular position in the nucleus were always seen. Very small chromatin blocks were observed peripherally but on the whole the chromatin condensation was slight The cytoplasm had sparse organelles besides polyribosomes, which diffusely filled the cytoplasm. Occasional strands of GER were usually demonstrable as well as single mitochondria and occasionally protolysosome like bodies. The cells were star-shaped with broad processes.

4 IF 2 cells. The diameter of the nucleus was roughly half that of the IF 1 cell (fig. 189) The nucleus had a very smooth outline but was often slightly indented A large nucleolus was seen in all these cells, most often in a central position in the

nucleus. It consisted mainly of a complex nucleolonema and the pars amorfa was less prominent The chromatin condensation was intermediate that of the IF 1 cell and the prolymphocyte The cytoplasm contained fewer polyribosomes and more GER than the IF 1 cell but only 1 or a few strands were seen in each sectional plane Occasionally there were parallel stacks or whorls of GER but it was never dilated (fig 194) Single cells contained a lamellar ribosome-studded membrane complex of the type seen in leukemic reticuloendotheliosis (hairy cell leukemia see survey in 28) (fig. 199) The mitochondria were more numerous in the IF 2 cells than in the IF 1 cells

The IF 2 cells had long processes which were often bifurcated and enclosed another cell process (fig. 189) The longer processes often had bundles of microtubuli and fine filaments (figs. 184 185) that were characteristically arranged along, and situated obliquely to the cell surface and sometimes inserting in desmosomes Desmosomal connections were also seen between short intertwining processes of such cells, and between such and the body of other IF 2 cells (figs. 196 198) and also prolymphocytes.

Most of the mitotic figures observed were obviously those of IF 2 cells, as judged from cell size and organelles (fig. 194)

Many IF 2 and IF 1 cells of case 2 219 contained bundles of wavy thread-like formations, which were round or irregular in cross section (figs. 203 204) No lumina were seen with certainty They were of uniform thickness and about 17 nm in diameter They were not related to the endoplasmic reticulum Sometimes they were seen close to membrane bound bodies containing polymorphous membranous material and electron opaque structureless material (fig. 203) Similar structures were seen in occasional cells in one of the cases of LLD-2 In some respects the structures resembled paramyxovirus, but it was not possible to characterise them more exactly in this poorly fixed material. No such formations were ever seen with in the nuclei Otherwise no structures were seen that resembled any virus component or other micro-organism In case 2 219 the mature lymphocytes contained numerous electron opaque bodies, about 0 3 μ in diameter surrounded by membranes and resembling so-called Gall-bodies Such bodies were abundant in the IF 2 cells and in prolymphocytes (fig 193) They were often seen in a small cluster of lysosome-like granules

In 8 9 69 the cytoplasm exhibited densities at various points of contact between the processes Within these areas the intercellular space was bridged by thin paired spicules (figs 150 151)

5 IF (and LLD ?) contained many cells with the following characteristics. The cell is hereinafter referred to as the IF 3 cell in spite of the fact that some similar cells were seen among the mature lymphocytes outside IF (as also single IF 2 cells and an occasional IF 1 cell were seen)

The size of the nucleus in the IF 3 cell was equal to that of the IF 2 cell but the nucleus was always elongated (figs. 190 191) The chromatin structures were similar but there was a stronger tendency to formation of a thin continuous layer of condensed chromatin under the nuclear membrane The nucleolus was often smaller These cells had a polarised cytoplasm and the cell body was elongated

tapering in direction from the nuclear pole (fig 190) From the body of the cell extended narrow branches that interlocked with the processes of the other IF-cells and showed desmosomes These cells were practically always associated with reticulin structures. These structures consisted of collagen-like fibril-bundles embedded in amorphous substance which was very electron opaque in the method used (fig 202) Similar fibrils were sometimes seen close to other cells but this may be due to incidental apposition. The cytoplasm of the IF 3 cells was "lighter" than that of the other cells because of the sparseness of polyribosomes. On the other hand there was a more abundant GER which differed from that of the other cells in that the strands were shorter and coarser (fig. 193) Mitochondria were abundant and the cells always contained bundles of fibrils more than the IF 2 cells also in a perinuclear position. Gall-body like granules of exactly the same appearance as in the IF 2 cells were often demonstrable in case 2 219 (fig. 193) It was obvious that these cells had features in common with reticulum cells. See also fig. 192

6 Macrophage-like cells These cells were irregularly distributed. The nucleus was characteristically irregular with deep clefts and pockets and the chromatin condensation was slight (fig. ?00) Often no nucleoli were seen. The cytoplasm was irregular in shape often polarised in a way resembling that seen in the IF 3 cells It contained abundant organelles of various types Numerous lysosomes were always seen and also phagosomes.

7 Case 2 219 was found to contain a small number of cells differing clearly from all other cells in the IF in that thev had an entirely smooth outline and no processes or interdigitation. They had a smooth outlined slightly ovoid nucleus and a small nucleolus. They were also recognized by their abundant lamellar GER and contained small lysosome-like granules. These cells resembled pro-plasmocytes (fig. 201)

8 All IF contained sparse examples of another type of cell with electron opaque nucleus often situated close to a vessel and with long processes with very electron opaque cytoplasm containing abundant GER and crowded monoribosomes and compact bundles of fibrils The processes were of astonishing length and extremely thin. Owing to their electron opacity they could be readily traced through the section, sometimes along a distance of several hundred microns (fig. 195) The processes were invariably associated with fiber structures. These cells were probably compressed fibroblasts.

9 Occasional cells with the appearance of ordinary interdigitating and dendritic reticular cells were met with. They had small nucleoli or no visible nucleolus in the plane of section The dendritic cells were connected by desmosomes to other similar cells (figs. 184 186 187)

THE VESSELS OF THE IF IF were rich in small vessels. On the light microscopic level one often had the impression that the IF was centered on a small vessel with a compressed lumen, often filled with a row of lymphocytes, and with a single row of low endothelial cells (fig. 211) The vessel was surrounded by a basal lamina of moderate width. High endothelium postcapillary venules were always seen in LLD-1 but these vessels seemed to be situated outside the small IF or often almost in contact with their periphery Venules of this type were seen within the larger IF

however and there did not seem to be any constant and typical topographic relation between the two structures (fig. 205) The narrow central vessel was sometimes seen to lead directly into a high endothelium venule and also those vessels were probably of a venous or capillary character From the electron microscopic point of view there was little to differentiate the two types of vessels except their size The endothelial cells had bundles of fibrils and other organelles which were of a similar character except that the high endothelial venular cells had more lysosomal granules than the low endothelium of the narrower vessel. In both vessels the basal lamina was split in the narrow one at least into two lamellae (fig. 212) in the high endothelium venules into many complex lamellae (figs. 205 206) Between them there was a layer of cytoplasm belonging to pericytic cells. This was often "clear" with few organelles, but occasional bundles of fibrils were always seen, and generally a few profiles of GER short and coarse like the reticulum of the IF 3 cells Typically pinocytic vesicles in large amounts were seen where these cells were apposed to the basal lamina (fig. 208) Within the laminar duplications many lymphocytes were seen in the venules (fig 207) A peculiar phenomenon was sometimes observed namely a clearing" of the cytoplasm when the cell passed a gap in the innermost lamella (fig 209) In some respects, then, the clear cytoplasm resembled that of the pericytes described above but true pinocytic vesicles were never seen in cells with preserved lymphocytic character It is here assumed that the lymphocytes pass from the lumen outwards. The other direction is of course possible but from what is known of lymphocyte traffic in the nodes generally it seems more reasonable to imagine passage outwards. The outermost lamina of the wall was thick and contained collagenous fibrils. The parenchymatous aspect had a moth-eaten appearance and many small blebs and gaps were seen through which lymphocytes were apparently travelling (figs. 205 208) The vessel was generally surrounded by a sheath of processes from cells with the characteristics of 5 and 8 above Those with the appearance of 5 were often but not always, partly invested in a thin duplication of the basal lamina trailing off into the parenchyma as a reticulum fiber (fig 212) Except for the pinocytic vesicles, these cells were similar to the pericytes. Sometimes they appeared to be pericytes breaking loose from the wall. In other places the cells of the parenchyma were directly and very closely apposed to the wall It was sometimes possible by serial sectioning to demonstrate desmosomal connections between IF cells of the parenchyma and cells within the laminar duplications of the vessel wall (fig. 208) Those cells appeared to be pericytes. In the light microscope it was sometimes possible to find venules with a large clump of tightly packed lymphocytes in the centre and where the wall seemed to be in a state of dissolution thus creating the impression that the venules could be transformed into parenchyma by lymphocyte stagnation

LLD . This examination confirmed the morphologic identity of the cells in this process and those of the IF of LLD-1 The prolymphocytes dominated the picture and IF 1 and 3 cells also were seen. A minor portion of mature lymphocytes was always found intermingled with the immature cells (figs. 213 214)

HL. Th gingival tumour in 669/73 and the pharyngeal tumour in 437/67 showed many artefact probably largely due to mechanical distortion at the time of

biopsy (performed with a small bioptome) The lymph node tumour of case 829/69 was better preserved and is dealt with first

The cellular picture was polymorphous with considerable variation in size and shape of cells and nuclei (fig. 156) Cells many times larger than lymphocytes dominated The nuclei were irregular with many invaginations and "pockets" (fig. 157) But also cells with a smooth nuclear contour and similar to IF 2 cells, were seen (fig. 158) Generally the nucleoli were multiple and consisted primarily of nucleolonema. The heterochromatin was moderately prominent and usually peripheral. The cytoplasm was abundant and contained large amounts of GER, partly in parallel formations (figs. 158 160) Many polyribosomes were also present The GER demonstrated occasional dilated sacks with structureless material. Bundles of thin cytoplasmic fibrils were seen most often in the cell periphery and situated obliquely or at right angles to the cell surface There were many groups of glycogen granules but mitochondria were not numerous. Many cells were surrounded with electron dense material including fibrils some of which demonstrated collagen-like cross banding. Thus, there was a close similarity of these structures to reticulum fibers (figs 159 160) Desmosomes were never seen, and only an occasional lysosome like body Mitotic figures were abundant (fig. 159) Many degenerating or dead cells were met with, often phagocytosed in the cytoplasm of histiocytes. The dead tumour cells often contained round intranuclear inclusions (fig. 155) with high electron density They consisted of granular or structureless material seemingly detritus

669/73 The general character of the nuclei was similar to that of the case described above but the chromatin condensation was less. GER was not so prominent still some profiles thereof were seen in every cell at the plane of section. An occasional parallel stack was seen, also such containing granular material of moderate density Peripheral bundles of fibrils similar to those described above were always seen. There were many vacuoles in the cytoplasm but they were probably artefacts.Occasional lymphocytes were seen intermingled with the HL-cells

437/67 The cells of this tumour seemed to be of a dual character Most of them had dark, lymphocyte-like nuclei of irregular shape with condensed chromatin, but with large nucleoli (fig. 76) Others had a larger nucleus with few chromatin clumps and a smooth contour The latter type of cell contained round inclusions in the cytoplasm, probably corresponding to the PAS-positive structures described earlier (fig. 76) They had a reticular substructure of alternating light areas and dark streaks. They were generally not seen within the membranes of the GER The dark cell type had markedly plasmacytoid features (fig. 77) Parallel formations of GER including granular material of moderate electron opacity were often seen (fig. 78)

The tumours of both of the last-mentioned cases contained many connective tissue fibers of varying thickness. They might be explained as pre-existing stroma of the tissue infiltrated by the tumour cells.

Chapter II

DISCUSSION OF THE IMMATURE CELLS IMMATURE FOCI OF THE LYMPH NODES AND MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE IN CHRONIC LYMPHATIC LEUKEMIA

Understanding of the histogenesis and progression of CLL appears to require elucidation of the nature of the immature cells of the IF and other tissues. The 2 most important questions in this connection are

1 What is the relation between the different types of immature cells, and between the immature cells and the mature lymphocytes, and

2 Is there any relation between the immature cells and the eventual development of HL?

As for question 1 three possibilities might be considered

A Are the immature cells precursors of lymphocytes?

B Are the immature cells descendants of lymphocytes possibly developed via a process analogous to that of immunoblastic transformation?

C Are the immature cells and the lymphocytes independent of each other cytogenetically but occurring with topographic association?

Here the scope of immature cells include prolymphocytes and the other types of immature IF-cells

A According to Lennert the nodes in CLL show pseudofollicular formations of lymphoblasts (36) Those are what I call IF Lennert calls them proliferation centers He thus probably regards the immature cells as lymphocyte precursors. There is in my opinion strong evidence in favour of this view For the immature cells are those of the CLL tissues which show mitotic figures The mature lymphocytes are presumably generated by mitosis, and even if they survive for a long time it must be possible to find the mitotic figures in their precursors The prolymphocytes, which are the dominating cells of the IF and mature lymphocytes have so many morphologic similarities that it appears reasonable to assume that one type is derived from the other As the prolymphocytes are the dividing cells they are reasonably the precursors An important question in this connection is whether the prolymphocytes are of the same nature in the blood and in all tissues. They are cytologically identical Although cytologic identity does not necessarily mean functional identity it seems improbable that a single morphologic type of cell corresponds to stem cells in the bone marrow and transformed lymphocytes in the lymph nodes, for example The prolymphocytes are also present in the blood although usually in low percentage and they can probably migrate between the various tissues. The prolymphocytes do not resemble the cells of so-called lymphoblastic leukemia of childhood an irrelevant point as the exact nature of the cells is uncertain in this disease Thus the prolymphocytes are according to this line of thought lympho-

cyte precursors. This assumption is also corroborated by the findings of IF n in the largest infiltrates and those organs most heavily infiltrated IF-n also contain prolymphocytes, though the more immature forms of IF-cells have gained predominance The large and atypical cells of IF n are reasonably dystrophic forms of IF 1 or IF 2 or IF 3 cells. It is difficult to find an explanation for IF-n occurring primarily in large infiltrates, unless they are themselves the site of origin of the lymphocytes of which the infiltrate consists. However little is known of the release kinetics from the tissue infiltrates. A counter-argument to the theory of the immature cells as lymphocyte precursors is that one cannot demonstrate any exact correlation between the WBC in the peripheral blood on one hand and on the other the extent of IF in the nodes and of immature cells in the marrow This relation however is dependent on the kinetics of cell division on the release mechanism and on cell death. The lack of correlation might be explained by the assumption that under certain conditions the immature cells proliferate without maturation and/or that the mature cells are not released to the blood The latter may well be the case especially after treatment when the WBC may be normal or low in spite of heavy tissue infiltration. Cases with a high percentage of immature cells in the marrow seem to have a tendency to reach very high values of the WBC at some point but they are not constantly at a higher level than other cases which may be interpreted as variation in the generation kinetics from time to time A further complication in the evaluation of the relation between tissue immature cells and the level of the WBC is that the prolymphocytes evidently are released into the circulation as such in considerable amounts in some cases, but not in others. LLD-2 which consists mainly of immature cells, may be aleukemic suggesting that these cells may be strictly tissue-bound in certain circumstances. The cells in question can, however sometimes pass into the circulation as such and give rise to the hematological picture of prolymphocytic leukemia. There is no sound basis for speculations about the cause of this variation in the behaviour of the immature cells. But the lack of a linear correlation between the WBC and the percentage of tissue immature cells cannot be used as an argument against the lymphocyte precursor theory Thus, the prolymphocytes probably generate the mature lymphocytes by division and maturation of one or both the daughter cells. What then is the origin of the prolymphocytes? It does not appear probable that they are lymphatic stem cells The low nuclear/cytoplasmic ratio is not the rule in stem cells, but is more compatible with an intermediate cell in a maturation chain If they were stem cells, they would probably be more profuse in the marrow than in the nodes. There are similarities to the IF 2 cells, at least electron microscopically and it appears reasonable that the prolymphocytes are derived from them See later discussion of electron microscopic findings.

As for alternative B the cytologic picture of the IF 1 and IF 2 cells suggest that this may be correct The low nuclear/cytoplasmic ratio is well compatible with a reactive lymphatic cell form The IF 1 cells certainly are very similar to normal immunoblasts as seen in a viral lymphadenopathy for example. Isomorphism is an unreliable criterion however But there are other factors to which I shall return later,making it reasonable to consider whether IF cells may not also be analogous

to plasma cell precursors.

The high frequency of mitotic figures in the IF 1 cells and IF 2 cells argues against alternative B What are the daughter cells after mitosis if they are not prolymphocytes or mature lymphocytes? If the IF-cells proper always and exclusively divided homoplastically the IF would reasonably expand rapidly because they show no signs of extensive cell death As the IF-cells proper are practically never seen in the blood they can not be released from the nodes as such. Large IF are sometimes seen in association with a low percentage of immature cells in the blood This can be taken as an argument for the mature blood lymphocytes being the products of the mitosis in the IF No true plasma cells are seen in the nodes of CLL, for which reason the IF-cells cannot disappear by conversion in situ into such

As for alternative C above It appears a priori less probable Why should a common tumour consist of unrelated cell lines in constant topographic relations? The origin of the lymphocytes would be enigmatic as would the slow or absent expansion of the IF in spite of frequent mitosis

Most evidence available thus suggests that IF are the origin of the circulating lymphocytes If this is so why should there be a relation between IF-n and monoclonal immunoglobulin components? IF n have so many similarities to the IF of biopsy specimens that it appears certain that they are advanced stages thereof But it appears incompatible with a theory of lymphocyte production in the IF that they show a correlation to monoclonal immunoglobulin components. It seems probable though unproved that the components are really produced by the cells of IF n, or their descendants.

It is theoretically possible to make a compromise between alternatives A and B namely that the IF-cells are both transformed lymphocytes and precursors of the mature lymphocytes. The latter should thus be B 2 (or occasionally perhaps T 2) cells originating from pathologic immunoblasts the IF-cells The IF 1 cell should then presumably be the immunoblast the IF 2 cells and prolymphocytes developmental stages towards B 2 cells The identity of the B 1 cell is enigmatic. It might possibly be a question of retransformation of leukemic cells thus a circular series of events in the CLL-process or clonal expansion by transformation of some other lymphocyte giving rise to a leukemic population of non-reactive cells.

It is pointless to construct an exact scheme of kinetics of such a speculative system but the B 1 population would presumably have to be of considerable dimensions to supply the pathologic process on rapid expansion of the B 2 pool unless the IF 1 cell once formed acts as a true stem cell.

Such a theory might explain the apparent contradiction between the IF-cell as lymphocyte precursor and as immunoglobulin producer if it be supposed that the immunoblast or its daughter cells can secrete immunoglobulins without assuming the morphology of the plasma cell

As for question n appears on morphological grounds probable that IF IF-n and HL are different stages of one and the same process. IF and IF n had the same topography and partly the same cell content Biopsy material rarely shows changes corresponding to those seen in IF n but this may be because the patient survives only a short time after the IF have assumed the more malignant character which

IF-n seems to imply Moreover biopsy specimens are rarely obtained from patients who appear to be in the terminal phase A lymph node biopsy specimen with a picture of both CLL and HL was observed in 1 case (829/69) and there very marked IF were seen with atypia which might correspond to IF-n IF-n and HL showed transitional forms. In extensive HL, IF n were not always seen, but all rests of such may have been eliminated by the more rapidly proliferating tissue All small HL lesions were surrounded by lymphocytes in such a way as to suggest that they had started in lymphatic infiltrates. HL in the liver always started in the largest lymphatic infiltrates, which were also the site of the most advanced IF-n. HL was seen less often in the bone marrow as were IF and IF-n. M-components occurred in the same frequency in patients with IF-n and HL, differing markedly from what was seen in cases without such changes, which also suggests a close relation between IF-n and HL.

Thus there is reason to suspect a relation between IF-cell and HL-cell. In the light microscope IF-cells are strikingly monomorphous. The morphology of the HL-cells might be divided into 3 groups, namely round basophilic cells of fairly uniform size (immunoblastic type) elongated fiber-associated often polymorphous cells and more bizarre cells which are often "histiocyte-like" and have abundant cytoplasm The last mentioned type occurs to some extent in tumours composed of one of the other two None of the HL-cases in the series showed exclusively one or the other cell type all forms occurring in varying proportions in all the cases. These types are probably variants of the same process. The immunoblastic type is obviously morphologically most closely related to the IF-cell. M-components often occur in association with the development of HL. This might be a reaction of some immunoglobulin-producing cell clone to HL. But the HL-cells often have an abundant GER with an organisation resembling that of plasma cells and they sometimes have an accumulation of substances similar to Russel bodies of plasma cells. As demonstrated by Stein et al. (65) HL often contains large amounts of immunoglobulins even in the absence of abnormal components in the plasma. All this suggests that the M-component is a product of the tumour cells. In those cases where the M-component was found long before the appearance of HL, it might be a question of immunoglobulin production in IF or in other types of lymphoma from immature cells analogous to IF-cells. If IF and HL-cells really can secrete immunoglobulins, they should belong to the B-cell system. According to the theory presented earlier HL should be seen as a block in maturation from immunoblast to B 2-cell. LLD-2/prolymphocytic leukemia might be a block at an intermediate stage

If the above theories are correct the terms HL and reticulum cell sarcoma must be inappropriate There are, however factors which are difficult to dismiss, and which argue for "histiocytes" or "reticulum cells" having something to do with this condition. First it should be emphasised that I now mean only HL developing in CLL. Primary HL lies beyond the scope of the present investigation

Pictures like the HL in case 961/61 suggest fibroplasia of the tumour cells. An abundance of fibers in the tissue is not per se a definite sign that the cells are of connective tissue character But when, as in this case there is an organised mode of

growth where the fibers and cells closely follow each other and the cells closely resemble connective tissue cells, it appears probable that it is a question of tumour cells with fibroplasia Also 42/65 showed a close structural relation between the tumour cells in the sinus and the fibrillar sinus reticulum. In this case the tumour cells appeared topographically like sinus endothelium and their behaviour also suggested a potential alveolar cell character The possibility of the tumour cells having a potential reticulum cell nature is dealt with in the discussion of the electron microscopical findings

An interesting problem is the relation between the clearly phagocytic macrophages and the tumour cells.The former might be a simple reactive phenomenon in association with tumour cell necrosis, for example Especially in the cases of Hodgkin s disease however they were so abundant that one wonders whether there was not some special relation between them There is no doubt that it was a question of a special topographic relation. The macrophages and Reed-Sternberg cells always appeared in association It appears probable that the Reed Sternberg cells in these cases are closely related to HL-cells Here a mention should be made of the literature on "Richter s syndrome" As pointed out in the introduction CLL followed by Hodgkin s disease appears to be at least as common as CLL HL. Many of the cases of Hodgkin s disease are classified as Hodgkin s sarcoma but judging from the illustrations, it is often a question of pictures which would equally well or even better fit in with the designation pleomorphic HL. Characteristic lesions of Hodgkin s disease with a granulomatous character and true Reed Sternberg cells are probably much less common than HL but it is obvious that they do occur in this connection I have seen another 2 cases of Hodgkin s disease eventually develop in patients with CLL (cases not part of this investigation. See fig. 120)

The morphologic findings in the studies of the IF are difficult to interpret Characteristically IF were distributed evenly and diffusely throughout the node They had no constant relation to pre-existing structures. The small vessels seen to penetrate them were so constant however that it is tempting to imagine some type of functional relation. Lymphocytes were seen to penetrate the wall and it appears that the cells leave the vessel to enter the parenchyma High endothelium postcapillary venules were also seen in all the biopsy nodes of CLL with a lively traffic of lymphocytes through their walls. One might imagine that the cells leaving the 2 types of vessels were different types of lymphocytes but they appeared morphologically similar

The great majority of the mitotic figures of the nodes in CLL were seen in the IF Occasional mitotic figures were seen outside the IF but so were occasional immature cells I do not think that the IF and the mature parts should be regarded as distinctly separate compartments The IF are rather local condensations of immature cells, especially prolymphocytes In the bone marrow the immature cells are generally not so focal in their distribution and are fairly sparse.Assuming that the immature cells are lymphocyte precursors the majority of leukemic cells should presumably be produ ed in the nodes. On the other hand the bone marrow as an organ is incomparably larger than the collected mass of the nodes in early CLL, which weighs against this assumption However the IF seem to be primarily nodal

structures. They may also be seen in the lymphatic tissue of the spleen and in the bone marrow but it was my impression that they appeared late in these organs, and were seldom so prominent as in the nodes. But they were often seen in the liver and therefore can not be a prerequisite of lymphatic organs in a restricted sense. Further they were occasionally seen in the renal hilar adipose tissue where lymphatic tissue is not indigenous.

The chief types of IF-cells have clear morphologic similarities Does this mean that they are genetically related? This is naturally impossible to prove from a fixed tissue section, but it is reasonable to assume that IF 1 cell IF 2 cell prolymphocy te and mature lymphocyte are subsequent generations in a process of maturation. Some of the organelles are identical, such as the Gall-body like structures and the thread-like formations. Also there is a relation in size between the cell types in question agreeing with such a hypothesis. If so the IF 1 cell is the most immature form of the leukemic lymphocyte I think it improbable that the direction of deve lopment is from the small lymphocyte of the parenchyma to IF-1 cell, primarily because of the ratio between their numbers. IF 1 cells are rather uncommon, IF 2 cells less so Supposing a high rate of mitosis, the development of an IF 1 cell into prolymphocytes and lymphocytes through IF ? cells could well be possible What then is the IF 1 cell? The possibility that it is a diseased stem cell cannot be exclu ded but I think it more probable that it is an abnormal immunoblast developed from some immigrant to the node If so it could be regarded as an intermediate cell in the disease process and a search should be made for a "pre-IF 1 cell" As specu lated earlier this might be a circulating lymphocyte expanding clonally into the leu kemic population. If this hypothesis is correct it should be possible to find cells intermediate between lymphocytes and IF 1 cells. The latter are so uncommon, however and the electron microscopic sections are so thin that this may be an ex tremely difficult task. The cells should probably be found in close proximity to the vessels. Candidates can be found, such as the cell illustrated in fig. 210 but natu- rally all this is hypothetic and impossible to prove by static morphologic observa tion. The events within the lymph node vessel walls could well be of interest in lymphatic malignancies.

What about the IF 3 cells then? They are certainly similar to reticulum cells with their long branching processes with fibrils and desmosomes. They could be mesenchymal stem cells and the precursors of the other IF-cells. But this seems improbable as they have more and higher specialised organelles than the IF 1 cells. Perhaps it can not be excluded that organelles disappear but it is not a promising hypothesis On the other hand IF 3 cells resemble IF 2 cells in various respects. The nuclear structure and the nucleolus are similar and they contain structures identical to the Gall-body like granules of IF cells and lymphocytes. Some of the IF _ cells have long processes and many of them have desmosomes. All this might be interpreted as signs of a genetic relation between these cells. If there is, it is more reasonable to assume that the IF 3 cells are derived from the IF 2 cells than vice versa as the IF 3 cells have more and higher developed organelles

If all this be correct the following state of affairs should prevail an immigrant to the node transforms into an immunoblast (IF 1 cell) within or close to the

vessel wall. Thus cell multiples by mitosis into IF 2 cells, thus creating the IF proper The IF 2 cell is a lymphocyte precursor but may also be a reticulum cell precursor All the IF-cells are descendants from the IF 1 cell When HL develops from the IF cells it may therefore have some characteristics of reticulum cell sarcoma Furt her the IF-cells could well be immunoglobulin producers if they are transformed B lymphocytes. The rare cells found in one case and illustrated in fig. 201 might be a remnant of plasmocytic differentiation generally almost totally absent This could explain the monoclonal immunoglobulin component in cases with prominent IF n and HL.

This theory thus infers that the pathological transformed cell (IF 1 cell) should have several developmental possibilities to mature lymphocytes via IF 2 cells and prolymphocytes, to tissue bound cellular elements reticulum cells" and to immunoglobulin secreting cells. The latter may possibly in this special pathological situation be morphologically very similar to IF 2 cells All thus is highly speculative and it appears useless to theorise about why the descendants of the IF 1 cells should sometimes choose one pathway sometimes another one The lymphocytic differentiation should be the most "benign" one while the others appear to imply a poor prognosis

It may be difficult to accept that reticulum cells are descendants of lymphocytic cells. The opposite is often held to be the case But reticulum cells are a heterogenous group and in some situations in adult life they must presumably be re-created from wandering cells In some respects the IF 3 cells resemble the dendritic reticulum cells of germinal centers In inflammatory reactions germinal centers may develop almost anywhere and in places where lymphatic tissue is not indigenous the reticulum cells thereof might well be derived from blood-borne precursors The IF 3 cells can certainly not be only the diluted rest of the original lymph node reticulum cells in the large nodes of advanced CLL. However evident IF 3 cells are much fewer than IF 2 cells. It is meaningless to construct an exact scheme of differentiation in this hypothetical model, but if it is somewhat realistic the IF 3 pathway must be much less frequent than the pathway of lymphocyte differentiation What is the ultimate fate of the IF 3 cells? It seems improbable that they are constant throughout the disease Once formed they probably persist for some time as IF 3 cells and then disappear either through death or by transformation into something else Otherwise the IF should probably expand more than they really do It is tempting to speculate that they are transformed into macrophage-like cells. There are some morphologic similarities, and this might explain the morphologic "histiocytic" tendency observed in some of the HL-cases. There is no doubt that the IF 3 cells are associated with reticulum fibers more often than other cells of the IF This may not prove that they produce these fibers, but it could explain the close association between connective tissue fibers and the cells of some of the HL-cases. No desmosomes were observed in the HL-cases examined This does not exclude a connection between IF-cells and HL-cells. A poorly differentiated spinocellular carcinoma also may lose the capacity of desmosome formation

Most studies of HL do not support a histiocytic origin of these tumours but rather suggest an immunoblastic nature Some cases have however demonstrated high activity of enzymes such as acid phosphatase and esterases, generally thought to belong to histiocytes and macrophages and also phagocytosis (see 17 22)

Microscopically indistinguishable tumours can be thought either to be derived from different cell types with final similar histology or to have identical histogenesis with differentiated biological function. The latter alternative might explain that morphologically identical tumours sometimes have immunoblastic characteristics but occasionally have histiocytic activity

As long as the transformed cells are capable of giving rise to differentiated cells, the conditions of CLL prevail. It is impossible to know what instigates the transformation of the presumed B 1 cell. It may be an internal abnormality and not an external agent. The leukemic B-2 cell population should be memory cells but they may have a "nonsense" memory without immunological function just as the M component could be a "nonsense" antibody If the capacity of lymphocyte differentiation is lost, HL might develop and the HL cells could then be the IF 1 cells in "malignant degeneration" but possibly with some preserved tendency to histiocytic and/or plasmacytic differentiation

The histologic picture of LLD-3 obviously has similarities to that of LLD-1 The cells however are more atypical and no IF are seen As LLD-3 in an early stage generally appears to be non-leukemic this sounds reasonable, because IF predominantly consist of prolymphocytes which according to what was previously said, probably are precursors of the leukemic lymphocytes. When HL develops in LLD-3 the type of cell is very similar to the HL in LLD-1 IF-n were not seen in cases of LLD-3 and the transformation to HL microscopically appeared to be more diffuse although, from a gross morphologic point of view focal in character Apart from the case resembling Hodgkin s disease the HL in LLD-3 was of predominantly immunoblastic type This argues for a close connection between LLD-1 and LLD-3 and also some cases from a cytological point of view appeared to be intermediate They are probably closely connected diseases, but nevertheless the vast majority of cases can be classified as one or the other Possibly they should be seen as clustering points on a continuous spectrum. But LLD-3 also had similarities to LLD-4 and one case was somewhat dubious as to classification LLD-3 or LLD-4 LLD-4 on the other hand, appeared to be a diffuse variant of LLN It would thus appear that all the lymphocytic (and also some histiocytic) malignant lymphomas are closely connected conditions. A case starting as a typical example of one type of lymphocytic lymphoma seldom appears to transform into another type of lymphocytic lymphoma (except for nodularity converting into diffuse growth) but all the types have a tendency to progress to the more malignant HL. All the lymphocytic lymphomas dealt with here contain immature cells in LLD-1 2 and 3 of the IF-cell type in LLD-4 and LLN morphologically somewhat different It appears probable that the immature cells are the precursors of the lymphocytic lymphoma cells in all the conditions in question and that the eventual development of HL occurs when the immature cells have lost their ability to form lymphocytes and divide homoplastically

Chapter 12

FINAL REMARKS ON NOMENCLATURE

No attempt will be made to suggest a new nomenclature for malignant lymphoma The one used consists of practical working terms. Several research groups have recently suggested new nomenclature systems see chapter 2 Many of those systems can be regarded as modifications of Rappaport s nomenclature Lennert in Germany has devoted much work to this problem for a long time and he has somewhat modified his terms from time to time At present Lennert recommends the so-called Kiel classification for which he is responsible to a great extent (20) Lukes & Collins system (42) and the Kiel classification can be regarded as quite new approaches to the problem and my findings will be briefly discussed in relation to them A detailed clinical trial should be undertaken before any new nomenclature is recommended for general use As far as I know no extensive clinical trial has yet been published where the Kiel classification and Lukes & Collins classification have been tested and compared Such studies are said to be in progress, and it is to be hoped that they will give unequivocal support to one system or the other so that an international agreement may be reached Rappaport s system has many disadvantages but at present it has the great advantage of being well understood in most countries Until an international agreement on a new system has been reached I do not think there is any reason to change any local deep rooted terminology in which the clinicians and morphologists can converse If such terms as reticulum cell sarcoma and lymphosarcoma are used it would be necessary in scientific work to describe more exactly which morphological picture is intended

As previously mentioned Rappaport s well differentiated diffuse lymphocytic lymphoma includes both CLL and aleukemic cases. In several materials the latter probably corresponds at least partly to what I have called LLD-3 My group LLD-2 is probably included in poorly differentiated diffuse lymphocytic lymphoma LLD-4 according to Rappaport also should be called poorly differentiated diffuse lymphocytic lymphoma The small-cell cases and such with very few blasts are difficult to classify according to Rappaport and correspond to what for example Dorfman calls well or poorly differentiated diffuse lymphocytic lymphoma. LLN is nodular lymphocytic malignant lymphoma according to Rappaport The term nodular is not recommended by Lukes & Collins or in the Kiel classification In these systems "nodular should be replaced by "follicular" This is based on the assumption that the nodules correspond to true follicles and germinal centers in normal lymphatic tissue Much argues in favour of this view and the term follicular may be better though to me nodular is acceptable as a strictly morphologic description, while follicular infers a certain patho-physiologic aspect of the classification which at present may be dubious

Rappaport s classification also includes a group of well differentiated lymphocytic lymphoma with morphologic manifestations of dysproteinemia. Some of the cases of LLD-3 and of macroglobulinemia should probably be included in this group which, however appears to be poorly defined morphologically

Lukes & Collins system has several chief groups according to the supposed physiologic character of the involved cells, for example T-cell types and B-cell types The B-cell types are those which are relevant in my study The subdivisions thereof are small lymphocytic type (CLL) plasmacytoid lymphocytic type follicular centre cell (FCC) type and immunoblastic sarcoma of B-cells. The FCC-type is further subdivided into small cleaved large cleaved small non-cleaved and large non-cleaved types. All of them may be follicular diffuse follicular and diffuse and sclerotic Sclerosis may be seen in many types of malignant lymphoma but especially in such as I have called LLD-4 and LLN It has been claimed to be a prognostically favourable sign but this aspect was not studied in my material as the cases were so few

LLD-1 is small lymphocyte type (CLL) LLD-3 probably should be called plasmacytoid lymphocyte In my opinion this is a misnomer as the tumour cells are not plasmacytoid in LLD-3 but lymphocytic cells typical and atypical. Many plasma cells are seen in the nodes and other tissues, but it has not been proved that they are part of the tumour proliferation. The picture of macroglobulinemia, however could be called plasmacytoid lymphocytic as intermediate cell forms are seen. My cases LLD-4 and LLN correspond to FCC-types the small-cell cases of LLD-4 to small cleaved FCC-type and the large-cell LLD-4 cases to large cleaved FCC-type Small and large non-cleaved FCC-types according to Lukes & Collins were not included in my study as they were referred to undifferentiated lymphoma and HL. Possibly however LLD-2 should have been referred to a non-cleaved type

My cases of HL presumably should have been classified as immunoblastic sarcoma Lukes & Collins classification also includes a group of histiocytic lymphoma however but according to the authors this is not well defined from a pure morphological point of view

It is thus evident that my groups have a close correspondance to those of Lukes & Collins classification. But I feel that the term plasmacytoid lymphocytic is not well chosen. My material was not large enough to warrant any conclusions as to whether it is meaningful to distinguish small-cleaved from large-cleaved lymphoma types.

The entities of the Kiel classification relevant to this study are the following.

A. Malignant lymphoma of low grade malignancy

1 Malignant lymphoma lymphocytic This group generally corresponds to CLL of the B-cell type The PAS-reaction is by definition negative
2 Malignant lymphoma, lymphoplasmacytoid (immunocytic) Lennert subdivides this group in three lymphoplasmacytic, lymphoplasmacytoid, and polymorphous. Most cases of immunocytic malignant lymphoma reveal PAS-positive globular inclusions in the cells.
3 Malignant lymphoma, centrocytic.
4 Malignant lymphoma centroblastic/centrocytic. This group includes all

follicular lymphomas.

B Malignant lymphoma of high grade malignancy

1 Malignant lymphoma centroblastic

2 Malignant lymphoma lymphoblastic.

3 Malignant lymphoma immunoblastic.

Some of my cases LLD-1 correspond to malignant lymphoma lymphocytic However the PAS-reaction in this group is according to Lennert by definition negative Thus, some of my cases LLD-1 which contained PAS-positive lymphocytic cells must by needs be referred to malignant lymphoma lymphoplasmacytoid (immunocytic) I do not think that this is reasonable Some of the cases like 258/68 (see fig 161 162) were clinically very characteristic CLL, and corresponded exactly to Lennert s descriptions of malignant lymphoma lymphocytic. A very occasional cell with PAS-positive globules of quite characteristic type was found however The patient had low immunoglobulin levels and no monoclonal component Thus, the case should be referred to malignant lymphoma lymphoplasmacytoid (immunocytic) of the Kiel classification only because of the occurrence of such PAS-positive cells. They may have to be searched for in many sections before found and I do not think that this single criterion is useful for a classification Instead I think that the occurrence of IF is more appropriate for defining a group of lymphocytic lymphomas corresponding to the clinical picture of CLL. It would include some cases with monoclonal immunoglobulin components within CLL According to Lennert monoclonal immunoglobulin components also by definition exclude CLL Lennert s opinion thus is that electrophoretic or histochemical demonstration of monoclonal immunoglobulin production is not compatible with CLL As far as I can see it has not been proved that all the tumour cells must be either producing or non producing If a very occasional cell can produce immunoglobulins such a distinction as made by Lennert is not useful and the difference between the two groups in question will be only relative But I also feel that LLD-1 and LLD 3 are closely connected conditions and it may well be that occasional cases have an intermediate morphology though my material did not present completely examined cases of such intermediate morphology Cytologically however the cases of bone marrow group 1 3 were intermediate in type and also clinically and they may well represent such conditions Thus I think that there are no strict boundaries between LLD-1 and LLD-3 or between the groups malignant lymphoma lymphocytic and malignant lymphoma lymphoplasmacytoid (immunocytic) of the Kiel classification According to Lennert the cell content of malignant lymphoma lymphoplasmacytoid (immunocytic) well corresponds to that of my group LLD-3 and atypical cells are described

One of my cases of LLD-3 (1147 65) in the biopsy specimens had a picture which corresponded well to the subgroup lymphoplasmacytic, while the necropsy specimens were of type polymorphous Thus this type is or may be a later phase of the lymphoplasmacytic type It is reasonable to assume that it is a developmental stage towards HL(malignant lymphoma immunoblastic)

According to Lennert the characteristic picture of Waldenström s macroglobulinemia is the malignant lymphoma with lymphoplasmacytic cellular picture That

is, clear lymphocytic and clear plasmacytic cells are present but no intermediate forms This was not the case in my material where all the classical cases of Waldenström s macroglobulinemia had a cell series with a smooth line of transition between lymphocytes and plasma cells. None of my cases with the picture corresponding to malignant lymphoma lymphoplasmacytic (LLD-3) had macroglobulinemia.

Malignant lymphoma centrocytic corresponds in some respects to the group of FCC-lymphoma, small cleaved type in Lukes & Collins classification. However this group in the Kiel classification does not admit the presence of any blastic cells at all. No such tumours were found in my material but the 2 cases of LLD-4 with few blasts otherwise resembled this group of the Kiel classification.

Malignant lymphoma centroblastic/centrocytic corresponds to all the other cases of LLD-4 and LLN It appears reasonable to have a common denomination for these processes with a specification of whether diffuse or follicular as the cellular content appears to be the same However the diffuse variant is probably much more often combined with leukemia Also the nodular variant may be more prone to develop HL.

The high grade malignant lymphomas of the Kiel classification correspond to Rappaport s groups of undifferentiated lymphoma and HL. Malignant lymphoma, lymphoblastic includes most cases of undifferentiated lymphoma. Malignant lymphoma centroblastic is the highly malignant growth developing in terminal phases of nodular lymphomas thus what I have included in the term HL in the course of LLN However it should be observed that the case of LLD-4 which developed HL had a characteristic immunoblastic picture Thus one can not generalise and say that malignant lymphoma centroblastic always represents the end phase of malignant lymphoma centroblastic/centrocytic and malignant lymphoma immunoblastic the end phase of malignant lymphoma lymphocytic or lymphoplasmacytoid But no case of my LLD-1 2 or 3 developed a picture of the type malignant lymphoma centroblastic, and it is probably the characteristic picture of the terminal phase of nodular lymphomas

Except for the cases resembling Hodgkin s disease all those called HL in the groups LLD-1 2 and 3 were partly of the type malignant lymphoma immunoblastic. The Kiel classification also acknowledges the existence of true histiocytic lymphomas, but they are not definable on a strict morphological basis.

The Kiel classification does not include any group corresponding to LLD-2

Thus my scheme agrees with the Kiel classification in that LLD-4 and LLN are variants of the same process, and that there is usually a certain difference between the anaplastic tumours developing after these conditions and after other lymphocytic lymphomas But I disagree with the Kiel classification in that CLL can be excluded morphologically by the presence of PAS-positive lymphocytic cells, at least when they occur in small numbers.

In Lennert s opinion most but not all case- of CLL have a "pseudo-follicular" histologic picture. My group LLD-1 was defined by the IF There was no lymph node biopsy without IF from a case clinically judged as CLL. As has been pointed out IF may be difficult to detect in necropsy specimens. But in all the cases of

LLD-1 in the necropsy series occasional IF or IF like structures could be found in some sections, though not in every section I therefore feel that IF are constant structures in CLL, but it may be true that not every node in every case contains evident IF Thus, it may be possible that occasional biopsied nodes in clinically CLL-cases may lack evident IF though the case belongs to LLD-1 Nevertheless, I think that prolymphocytes and IF-cells can always be found and the slight or absent atypia of the mature cell component should always make it possible to distinguish LLD-1 from LLD 3 in biopsy specimens

The presence of monoclonal immunoglobulin components excludes CLL in the Kiel classification In many of my cases of LLD-1 (also without PAS-positive lymphocytic cells) no monoclonal component was found initially but it appeared later on According to the Kiel classification such cases should thus be called malignant lymphoma lymphocytic converting into malignant lymphoma lymphoplasmacytoid (immunocytic) This appears cumbersome and unnecessary

The terminological problems bearing on macroglobulinemia are complicated In the early phases of this disease the lymph nodes are generally not enlarged and it is a question primarily of a bone marrow infiltration Generally however there is some slight infiltration of the nodes and they may be somewhat enlarged later on From a practical point of view it may be unsuitable to designate the disease as a malignant lymphoma But this is a semantic question I seriously doubt the existence of Waldenström s macroglobulinemia without bone marrow infiltration. The disease could certainly be called lympho-proliferative The characteristic cytologic picture is a mixture of lymphocytes, plasma cells and intermediate forms. No cytologic picture of this very type was found in any bone marrow smear in my series without the clinical picture of Waldenström s macroglobulinemia It cannot be excluded that occasional such cases exist but they must be rare As pointed out above I think that plasmacytoid lymphocytic lymphoma (Lukes & Collins) is an acceptable description of the picture In the Kiel classification it could be called malignant lymphoma immunocytic of lymphoplasmacytoid type but should not be designated lymphoplasmacytic type Waldenström s macroglobulinemia should be used as a designation for a biochemical abnormality and a clinical syndrome and not as a morphologic diagnosis. The morphologic examination of the condition will presumably also in the future be performed primarily by cytologic examination of the bone marrow One may perhaps use the term "cytology of immunocytoma type with a picture compatible with Waldenstrom s macroglobulinemia Anyhow it appears that the disease is a malignant condition of lymphocytic cells closely related to other forms of lymphocytic malignant lymphoma The clinical features justify the retention of the term Waldenstrom s macroglobulinemia even if it should not be used as a morphologic diagnosis

SUMMARY

This study concerns the interrelationship between lymphocytic malignant lymphoma and lymphatic leukemia and an investigation of the morphologic and clinical course of some types of lymphocytic lymphoma and leukemia from the time of diagnosis to death. Cases with Waldenström s macroglobulinemia were also studied

A historical review is given of the lymphoma-leukemia problem complex as well as of the literature on terminal transformation to other types of lymphoma in chronic lymphatic leukemia (CLL) and other types of lymphocytic malignant lymphoma A brief outline is presented of different opinions of the nature of Waldenström s macroglobulinemia.

The material consisted of necropsied cases of malignant lymphocytic diseases in adults from Malmö (population about 250 000) during 17 years.

A simple lymphoma nomenclature based on Rappaport s well-known terms was used The term "differentiation" was, however excluded. The following chief groups were used lymphocytic malignant lymphoma diffuse (LLD) lymphocytic malignant lymphoma, nodular (LLN) malignant lymphoma of histiocytic type (HL)

LYMPH NODE BIOPSY STUDY The lymphocytic lymphomas were studied histologically in a biopsy series of 41 cases. They were assigned to the following groups

LLD-1 this was found to be the characteristic picture in CLL. Histologically the node consisted mainly of small lymphocytes with no apparent abnormalities. There were however foci of immature cells (immature foci, IF) made up of larger cells with nucleoli but still with a lymphocytic character They were called prolymphocytes. Further the IF contained still larger cells with very prominent, centrally situated nucleoli.

LLD-2. these nodes were dominated by prolymphocytes and also contained the larger cells of the IF described above but no evident IF as this immature tissue made up the whole node The picture was interpreted as corresponding to the hematologic condition called prolymphocytic leukemia.

LLD-3 the cells were of the same size as the small lymphocytes of LLD-1 or slightly larger The mature cell component was always somewhat atypical. Immature cells similar to those described above were present but they were also generally somewhat atypical and no IF were present.

LLD-4 the dominating cell was lymphocytic in type but had an irregularly shaped nucleus (such cells were called atypical) Also larger blastic cells were present but they differed in appearance from those in the preceding groups.

LLN tumours with well-formed nodules resembling true follicles of normal lymphatic tissue The nodules had a cell content similar to that of LLD-4

The distribution among the groups was as follows

LLD-1	13 cases
LLD-2	2 cases
LLD 3	7 cases
LLD-4	13 cases
LLN	6 cases
Total	41 cases

The age and survival of the different types are given The groups were too small to reveal any statistically significant differences

LLD-1 always appeared to be a systemic disease when diagnosed This also applied to LLD-2 LLD-3 also generally appeared to be generalised but in occasional cases the bone marrow was spared LLD-4 and LLN often appeared to have a localised stage before dissemination

The leukemic manifestations of the various groups are described LLD-1 always was leukemic at the time of the diagnosis. One of the 2 cases of LLD-2 was non-leukemic None of the cases of LLD-3 was leukemic at the time of diagnosis, but 4 of 7 had absolute lymphocytosis LLD-4 generally was without abnormal values in this respect but a few cases had leukemic values and some others had absolute lymphocytosis without leukemic values of the WBC Five of 6 cases of LLN had normal blood values, only 1 had absolute lymphocytosis and none was leukemic.

During some period in the course of the disease all cases of LLD 1 and LLD-2 were leukemic while 4 of 7 cases of LLD-3 had clearly leukemic values and 6 of 7 had absolute lymphocytosis during some period In LLD-4 8 of 13 had leukemic values during some period and 10 of 13 had absolute lymphocytosis during some period In LLN no patient had clear leukemia but 2 had absolute lymphocytosis during some period.

All the patients in LLD-1 and LLD-2 had bone marrow infiltration at necropsy and the majority but not all of the cases in the other groups

The cytologic appearance of the blood and the bone marrow in the various groups is described

The immunoglobulin values in the clinical records were examined The characteristic finding in LLD-1 was low values, while all the examined cases of LLD-3 initially had high values Monoclonal immunoglobulin components were seen in both groups In the other groups the immunoglobulin values were less consistent

All the cases had been examined with a complete necropsy Generalised involvement was the rule in LLD-1 and 2 The majority of cases of LLD 3 also had generalised lesions at necropsy though in occasional cases the bone marrow and occasional nodes seemed to have been spared No soft tissue or parenchymatous tumours were seen in LLD 1 2 or 3

In LLD-4 disseminated disease was also generally found at necropsy but occasional cases had no infiltration of the spleen or liver Some also had normal lymph nodes in some sites. Many cases had extra lymphatic tumours.

All the cases of LLN had had lymph node engagement in all sites at the time of death Spleen liver and bone marrow were spared in some cases. Most of the cases had extra-lymphatic tumours.

Some case histories are related to illustrate the natural history of the lymphoma groups. It is concluded that LLD-3 often had a prolonged prediagnostic stage during which the blood picture was normal or almost normal. Later on the majority of cases developed atypical lymphocytosis and many a clearly leukemic picture. Many of the patients developed HL before death.

Some of the cases of LLD-4 also appeared to have a prolonged pre-stage with few or no clinical symptoms. Cases with small lymphocytic cells and few blasts appeared to have the best prognosis. A leukemic blood picture sometimes occurred and lasted for more than 2 years, but in most cases such a blood picture appeared only during the last few months of life

Also some cases of LLN reported a long preclinical history HL often developed terminally in this group

The findings were interpreted as follows LLD 1 (CLL) and LLD-2 (prolymphocytic leukemia) are closely related systemic diseases ("lymphocytic leukemias proper") LLD-4 and LLN are variants of the same disease (" the lymphocytic lymphomas proper") LLD-4 is probably seen more often with a leukemic blood picture however LLD-3 is difficult to classify as either lymphoma or leukemia and appears to occupy an intermediate position. A division of the lymphocytic malignant diseases into leukemia and lymphoma is not very useful. In the leukemic phase LLD-3 had many similarities to CLL but regarded as groups, there were many differences between the 2 conditions.

EXAMINATION OF BONE MARROW SMEARS INTERPRETED AS LYMPHATIC LEUKEMIA OR LYMPHOCYTIC LYMPHOMA In 79 of the necropsy cases technically acceptable smears of bone marrow obtained during life were available. They were studied in May-Grünwald-Giemsa staining. A group (bone marrow group 1) was judged as characteristic of CLL based on a predominance of apparently normal or almost normal lymphocytes mixed with a low percentage of prolymphocytes.

A group (bone marrow group 2) was distinguished where more than 50 % of nucleolated lymphocytic cells of prolymphocytic type were seen. A group of smears (group 3) was judged as lymphocytic lymphoma of non-leukemia type. It was found difficult to distinguish the pictures of LLD 3 LLD-4 and LLN with certainty and they were pooled in one group which also included some cases with a similar bone marrow picture but with the histologic picture of undifferentiated lymphoma in biopsy or necropsy specimens.

A group of smears (group 4) probably represented Waldenström s macroglobulinemia as judged from cytologic characteristics described in the text

Occasional cases could not be classified in any of the above mentioned groups. Some cases appeared to be intermediate CLL and group 3 (group 1-3)

Forty-two cases were judged as CLL (group 1) Clinically they were all leukemic at the time of the diagnosis and all of them had the clinical diagnosis of CLL. Figures for age and survival were approximately the same as for LLD-1 in the lymph node biopsy material. Some of the cases had HL or Hodgkin s disease in the necropsy specimens. No clinical or hematologic parameters could be detected to warrant a distinction of those cases from other cases of CLL.

Generalised lesions in the necropsy specimens was the rule Occasional cases had tumorous collections of lymphocytes outside the lymphatic system

Group 2 (12 cases, suspected as prolymphocytic leukemia) did not clinically differ perceptibly from group 1 There was a higher percentage of cases with many immature cells in the peripheral blood but some cases had a fully mature blood picture Generalised lesions at necropsy was the rule Three of the cases had a remarkable picture in the necropsy specimens wi h — use lymphocytic infil fibrosis.

The ca s y as either CLL or lymphocytic malignant lymp oma of non leukemic type had no clinical characteristics in common They resembled either the type of disease seen in LLD-1 or LLD-3

All the cases judged as suspect Waldenström s macroglobulinemia had this clinical diagnosis

The group judged as lymphocytic lymphoma of non-leukemia type wa t to separate into LLD 3 LLD-4 LLN

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tures w y be lymphocytic though atypical. Th eristic feature of LLD-4 and LLN was a highly irregular shape of the nuclei but apparently normal lymphocytes may also be found Cytologically the border towards LLD-3 was diffuse The smears from non-leukemic lymphocytic lymphomas were often technically poor making it even more difficult to distinguish the said conditions from each other

It is concluded that the lymphocytic leukemias and Waldenström s macroglobulinemia can be diagnosed with reasonable certainty from routinely stained bone marrow smears In cases judged as non leukemic lymphocytic malignant lymphoma exact classification of the bone marrow picture is difficult if not impossible Classification of such cases requires lymph node biopsy

TOTAL NECROPSY MATERIAL Sixty patients were not examined with either biopsy of the lymph node or bone marrow aspiration The majority 45 cases, were judged as LLD-1 Only 2 cases were judged as LLD 3 Technical difficulties are met with in the classification of the diffuse lymphomas in necropsy specimens if autolysis has taken place Generally however correct classification will be possible if many sections are examined

Broadly speaking the findings in the necropsy material confirmed what had been found in the series of lymph node biopsies and bone marrow smears. The reason for the difference in the prevalence figures among the groups in biopsy and necropsy series is discussed It is proposed that LLD-3 is seen much less often in necropsy series than in biopsy series because a large number of such cases have transformed to HL before the death of the patient

Among cases linically judged as CLL the frequency of malignant tumours of non-lymphatic type did not differ significantly from that of the entire necropsy material of the institute

A SERIES OF CASES CLINICALLY DIAGNOSED AS WALDENSTRÖM S MACROGLOBULINEMIA Nine cases had this clinical diagnosis. Six of them had a classical bone marrow cytological picture They were clinically very benign One of them died after 180 months of HL. Lymph node enlargement was otherwise not a feature of the disease though most but not all of the patients had microscopic lymph node lesions at necropsy The histologic picture resembled LLD-3 but the cytologic picture was different in that only few or no atypical immature cells were seen and the nodes were dominated by lymphocytes, plasma cells and intermediate cell-forms. Occasional immature cells were always seen.

Three cases with a clinical diagnosis of macroglobulinemia deviated considerably from the above cases. One of them had a plasmacytoid and blastic, focal proliferation in the bone marrow but no lesions of the lymph nodes. Another one had the blood picture of CLL but a histologic picture of the tissues compatible with other cases of macroglobulinemia At splenectomy a small focus of HL was found in the spleenInanother patient, the disease was clinically characterised primarily by pulmonary infiltration This patient had 3 monoclonal immunoglobulin components, IgM IgG and IgA In the bone marrow there were focal infiltrates with central fields of lymphocytic cells, surrounded by fields of plasmacytoid cells and plasma cells

It is concluded that most cases of Waldenström s macroglobulinemia have a characteristic cytologic picture of the bone marrow Lymph node enlargement is not a feature of the early phases of the disease Occasional cases with this clinical diagnosis have morphologically deviating features Hematologically a picture of CLL may be seen The morphologic picture of the tissues is still lymphoplasmacytoid, however Thus, Waldenström s macroglobulinemia cannot be used as a morphologic diagnosis. The picture of the tissues is mostly but not always, of a lymphoplasmacytoid type HL may develop terminally in macroglobulinemia probably not so rarely *Macroglobulinemia should be regarded as a malignant lympho-proliferative* disease closely related to other lymphocytic malignant lymphomas, but in the early phases it is primarily a disease of the bone marrow

A STUDY OF THE IMMATURE CELLS IN LLD-1 IF varied widely in size and number in the lymph nodes. They contained mature lymphocytes prolymphocytes, which were generally the dominating type of cell a moderate amount of larger round cells with a prominent centrally situated nucleolus and moderately basophilic cytoplasm (called IF 2 cells) Further an occasional very large strongly basophilic cell with many large nucleoli was seen (called IF 1 cell)

All the cases with IF in the series had a leukemic blood picture at the time of the diagnosis. IF were therefore regarded as characteristic of CLL. The amount of IF however was not directly related to the values found for WBC in the peripheral blood nor was the amount of the above mentioned immature cell types in the bone marrow directly related to the level of the WBC Cases with a high percentage of immature cells in the peripheral blood had a tendency to reach very high maximal values of WBC and had a worse prognosis than cases with predominantly mature blood picture They corresponded approximately to the prolymphocytic leukemia

of the literature. This hematologic picture may be seen in LLD-2, but probably also in LLD-1 with large IF. LLD-1 (CLL) and LLD-2 (prolymphocytic leukemia) are interpreted as variants of the same disease.

For technical reasons IF were sometimes difficult to detect in necropsy specimens. However, they were generally demonstrated when many tissue sections were examined in cases hematologically characteristic of CLL. Sometimes very prominent IF-like foci with large and atypical cells were seen in necropsy specimens from such cases. They were called IF-necropsy (IF-n). Such foci were seen in 24 of 94 CLL-cases. IF-n showed no sharp border with microscopic HL lesions. IF-n were primarily seen in central lymph nodes and the liver, not so often in the spleen or the bone marrow and seldom in other tissues. IF-n were primarily seen in very large nodes and large tissue infiltrates in the liver. All cases with IF-n in the liver and in the spleen had marked enlargement of these organs.

Cases demonstrating IF-n in the necropsy specimens had no clinical or hematologic characteristics differing from those of other cases in the series. In the vast majority of cases where IF-n were found the patients had died of lymphoma, but in those who died from some other cause IF-n were seen in only few cases. The average survival of cases with IF-n was longer than that of cases without such lesions and it is concluded that IF-n are a sign that the disease had approached its natural terminal phase. Monoclonal immunoglobulin components were seen more often in cases with IF-n in the necropsy specimens than in others. Such monoclonal components often occurred only late in the course of the disease. It is concluded that the appearance of a monoclonal component in CLL may be a bad prognostic sign.

A STUDY OF CASES WHICH DEVELOPED MALIGNANT LYMPHOMA OF HISTIOCYTIC TYPE IN THE COURSE OF CHRONIC LYMPHATIC LEUKEMIA. In the CLL series of 94 cases necropsy revealed Hodgkin's disease in 2 and HL in 10. For practical reasons, the cases of Hodgkin's disease are included within the scope of the term HL below.

The HL-cases did not survive a shorter time after the diagnosis than other cases in the series. Only in 2 of the patients the diagnosis was made before necropsy. Clinically, the cases were characterised by a very rapid downhill course during the last year before death. Fever was almost universally seen. The organ affected by HL at necropsy had always grown rapidly in the final phase. No signs could be detected of any special type of treatment having precipitated the development of HL. There was no characteristic hematologic reaction pattern to treatment of CLL in those cases which eventually developed HL. Most of the cases were still leukemic at the time of death. Monoclonal immunoglobulin components were common among the patients developing HL. One of the patients also had characteristic multiple myeloma.

Symptomatic HL lesions often appeared in the throat or air passages. However, it is concluded that HL transformation probably takes place in many sites in the body at approximately the same time in most cases. Extra lymphatic tumorous lesions generally developed. The liver was affected more often than the spleen or the bone marrow. At least one of the HL-cases had a morphologic picture characteristic of Hodgkin's disease and another one a picture best fitting in with the dia-

gnosis of Hodgkin s disease though somewhat atypical Otherwise the HL-cases histologically and cytologically were primarily of so-called immunoblastic type Three of the cases, however morphologically were suspect of "histiocytic" differentiation of the cells.

In the other lymphoma groups of the necropsy series, also HL-cases were seen. LLD-3 appeared to be the group most often affected by this terminal complication. Also in this group the cases were primarily of immunoblastic malignant lymphoma type but a case with a picture suspect of Hodgkin s disease was seen. The clinical picture in the terminal phase of the disease was similar in this group to that of the LLD-1 cases developing HL.

One of the LLD-4 cases also developed HL of typical immunoblastic type This case from the beginning had some similarities to LLD-3

HL was seen in 6 of 13 cases of LLN These cases are not described in detail.

SPECIAL MORPHOLOGIC STUDIES OF IF AND HL. Some special staining methods were used in cases of HL and LLD-1 They were not very rewarding. PAS-positive inclusions within lymphocytic tumour cells may be seen also in cases otherwise quite characteristic of LLD-1 (CLL) and in the absence of monoclonal immunoglobulin components

Electron microscopic investigation of the IF demonstrated very complex surface relations between the cells with intertwining processes. They were sometimes connected by desmosomes in the IF 2 cells. IF 2 cells contained occasional strands and whorls of granular endoplasmic reticulum IF 1 cells were found only after prolonged search. They were electron microscopically characterised by many free ribosomes and polyribosomes.

Another cell type was seen, which had similarities to IF 2 cells and which was difficult to distinguish from such in the light microscope It had a polarised cytoplasm with extensions with desmosomes and resembled in some respects reticulum cells.

An electron microscopic study of some cases which had developed HL was performed The cells had similarities to IF-cells but were more anaplastic. Some similarities to reticulum cells were also seen.

In the DISCUSSION 2 questions are primarily dwelt upon, namely whether there is any connection between the immature cells of the IF and the mature lymphocytes of CLL. It is concluded that there probably is and that the IF 1 cell should be regarded as the "first" cell in the CLL-process and that IF 2 cells and prolymphocytes are descendants thereof It is proposed that the IF 1 cell is a pathologic immunoblast and an immigrant to the node through the lymph node vessels. Thus, the mature lymphocytes of CLL should be B 2 cells. What is the B 1 cell is speculative

Further it is discussed whether there is any connection between the IF and the terminal development of HL. It is concluded that such a connection exists and that the HL-cells are the IF-cells "in malignant degeneration" It is proposed that the assumed pathologic immunoblasts (IF 1 cells) have several developmental possibilities One of them is the possibility to produce small lymphocytes (the mature cell component of CLL) another possibility is to differentiate into immunoglobu-

lin producing cells. This might explain the appearance of monoclonal immunoglobulin components when HL is developing. Further it is speculated that the IF 1 cell may have a possible pathway towards reticulum cells possibly of the dendritic type or towards macrophagic cells. This might explain a morphologic "histiocytic" tendency and a fibroblastic tendency in some of the HL-cases developing in the final phase of CLL.

The findings are discussed in relation to some new nomenclature systems of malignant lymphomas

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MICROSCOPIC REPRODUCTIONS

Unless otherwise stated all cytologic specimens were stained with May-Grünwald-Giemsa and the illustrations of them are magnified 1120 x, and all illustrations of histologic appearances are of specimens stained with hematoxylin and eosin.

The electron microscopic photographic recording was done on cut film in a Philips 300 electron microscope All electron microscopic enlargements are approximate.

The necropsy number of the case to which the illustration refers is given only if the case is described in the text

Fig. 1 Low power view of lymph node in LLD 1 with large immature foci (IF) The IF appear as lighter fields. Case 829/69 Giemsa x 30

Fig 2 Transitional zone between IF (to the right) and mature part (left) Note *difference in cell size between the prolymphocytes, which dominate the right side* of the reproduction and the mature lymphocytes to the left Large immature cell at asterisk IF 1 cell (see chapter 8) at arrow Mitotic figures left centre They are often most numerous in the periphery of the IF Case 829/69 Giemsa, x 540

Fig. 3 LLD-1 Mature part. The picture is dominated by small mature lymphocytes. Only occasional prolymphocytes. Biopsy case 2 219 x 1120

Fig. 4 LLD-1 Cell content of IF Several large immature cells (IF 2 cells see chapter 8) are seen e.g. at asterisk. Most other cells are prolymphocytes (e.g. at arrows) Occasional mature lymphocytes. Biopsy case 2 219 x 1120

Fig. 5 Blood smear with lymphocytes and a prolymphocyte from case with LLD-1 (185/63)

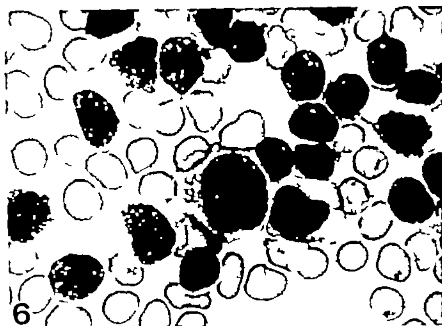

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Fig 6 Bone marrow smear from case with LLD-1 (185/63) Lymphocytes, prolymphocyte and large immature cell.

Fig. 7 Smear of fine needle aspirate of lymph node in LLD-1


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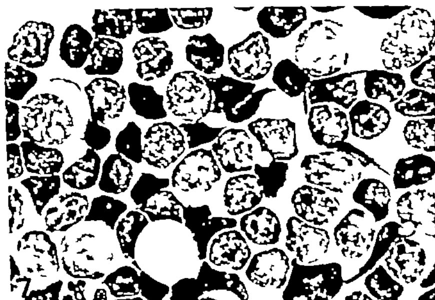
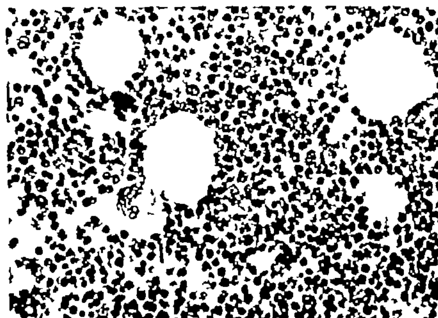

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Fig. 8 Section of aspirated bone marrow particle in LLD-1 demonstrating diffuse infiltration with predominantly mature lymphocytes without IF Large cells are megakaryocytes. Some remaining fat cells Case 31/67 x 450

Fig. 9 Higher magnification of bone marrow section from case 31/67 (LLD-1) demonstrating an occasional prolymphocyte and large immature cell (centre) scattered among mature lymphocytes. x 1120



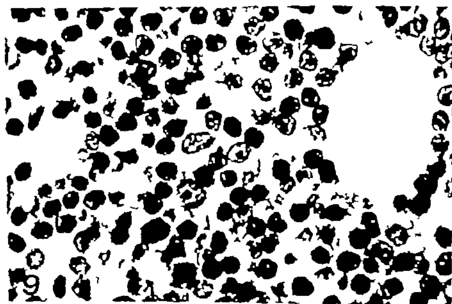
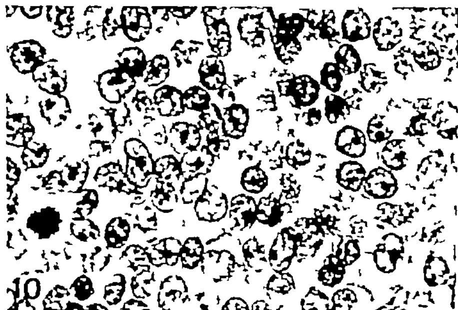


Fig. 10 LLD-2 Section of lymph node demonstrating large immature cells and predominance of prolymphocytes but only few mature lymphocytes. Mitotic figure to the left Case 663/58 x 1120

Fig. 11 Fine-needle aspirate from the same node as in fig. 10


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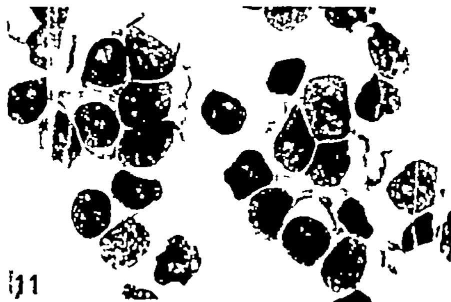

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Fig. 16 Fibrosing portal infiltrate of the liver in case 663/58 (LLD-2) x 100

Fig 17 Cytologic bone marrow picture of case 671/66 (LLD-2) Many prolymphocytes and mature lymphocytes.

Fig. 18 Bone marrow group 2 (case 151/65) demonstrating prolymphocytes and occasional mature lymphocytes in bone marrow smear Compare fig. 19

Fig. 19 Blood picture of case 151/65 on same occasion, demonstrating only mature lymphocytes. Compare fig 18


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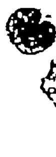

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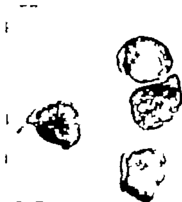
Fig. 20 LLD 3 Lymph node biopsy specimen from case 705/70 Somewhat atypical large immature cells and small partly somewhat atypical lymphocytes. No IF Giemsa x 530

Figs. 21 22 and 23 LLD-3 Bone marrow smear from case 705/70 demonstrating atypical lymphocytes.

Figs. 24 and 25 Blood picture of case 705/70 (compare figs. 21 23) Atypical cells, some with cleaved nucleus.

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Fig. 26 LLD-3 Section of aspirated bone marrow particle from case 1147/65 Rather dense but unevenly distributed infiltration of predominantly small and mature lymphocytes. x 450

Fig. 27 Bone marrow smear from case 1147/65 demonstrating mature atypical cells clustered around histiocytes.

Fig. 28 LLD-3 Electron micrograph from section prepared from same block as fig. 26 Note predominantly mature appearance of cells, but many with deep clefts and generally irregular shape of the nucleus. G = granulocytes. x 5700





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Fig. 29 LLD-3 Bone marrow smear of case 1140/71 demonstrating small group of atypical but predominantly mature lymphocytes.

Fig. 30 LLD-3 Lymph node biopsy specimen from case 1140/71 demonstrating large immature cell and partly atypical lymphocytes x 1120

Fig. 31 Necropsy specimen of lymph node from case 1140/71 (LLD-3) demonstrating lymphocytic infiltrates at the hilus of a lymph node with small focus of large-cell tumour with a slightly granulomatous appearance resembling Hodgkin's disease x 180

Fig. 32 High magnification of the tissue resembling Hodgkin's disease of fig. 31 x 450


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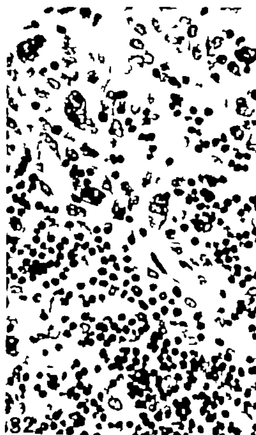

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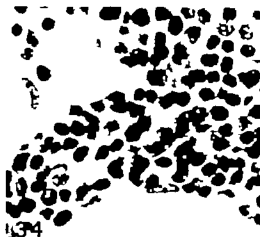
Fig 33 LLD-3 Section of bone marrow particles from case 1120/60 Dense but uneven infiltration of lymphoma. x 55

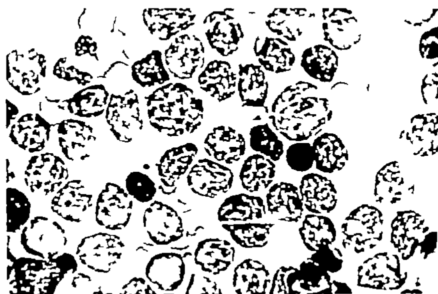
Fig. 34 Higher magnification of fig. 33 Atypical but predominantly mature lymphocytes. x 800

Fig. 35 Smear of bone marrow aspirate from case 1120/60 Compare fig 34

Fig. 36 Atypical cells in the peripheral blood from case 1120/60


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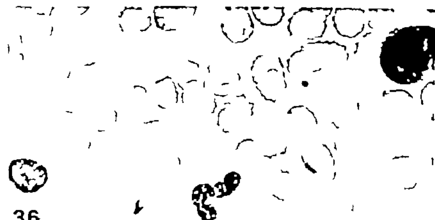
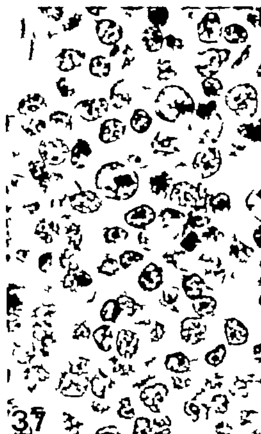

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Fig. 37 Lymph node biopsy specimen of case 1120/60 (LLD-3) demonstrating large immature cells and both atypical and apparently normal lymphocytes x 1120

Fig. 38 Appearance of a lymph node in the necropsy specimens of case 1120/60 demonstrating HL. Compare fig. 37 x 1120

Fig. 39 LLD-3 Splenic aspirate from case 220/72 Lymphocytic cells of varying atypia and maturity


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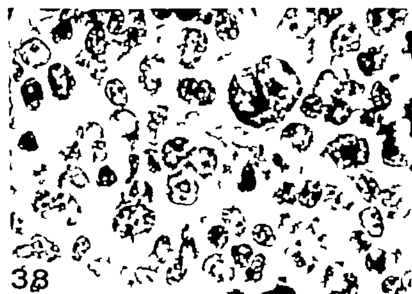
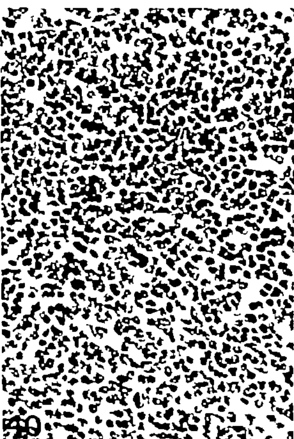

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Fig. 40 LLD-4 Section of lymph node biopsy specimen of case 451/61 Possibly faint tendency to formation of a follicle in lower part of illustration No large immature cells similar to those of LLD-1 2 or 3 x 450

Fig. 41 High power view of fig 40 demonstrating irregular shape of cells and very few apparently normal lymphocytes. One large immature cell x 1120

Fig 42 Same lymph node as figs. 40 and 41 stained with methyl-green and pyronin. Note many intensely stained plasma cells (indicated by arrows) Occasional blast cells (asterisks) x 1120


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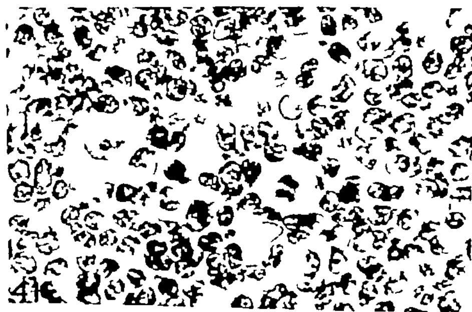

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Fig 43 Bone marrow smear from case 451/61 Some cells with irregular-shaped nuclei, but nuclear contour often rounded or oblong. Nucleolus variably visible.

Fig. 44 LLD-4 Peripheral blood from case 619/64 Atypical nuclei but preponderantly mature structure Many of the cells have a notched" appearance This type of cell is not specific of nodular lymphomas but occurs also in LLD-4

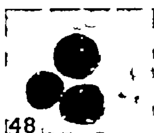
Figs 45 and 46 LLD-4 Bone marrow smear from case 963/66 Irregular generally somewhat immature nuclei with varying visibility of nucleolus

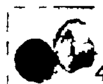
Figs 47 and 48 LLD-4 Blood picture of case 963/66 Cells are essentially similar to those in bone marrow (figs. 45 and 46)



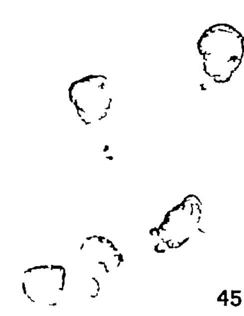
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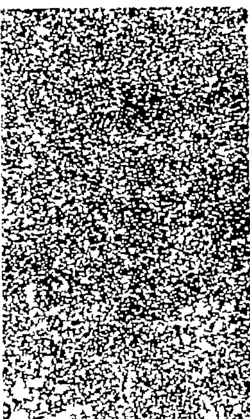


Fig. 49 LLD-4 Lymph node biopsy specimen from case 535/62 Slight "cloudiness" faintly resembling nodularity but no well-formed follicles In low magnification the picture may be mistaken for IF but readily recognized by high power scrutiny x 75

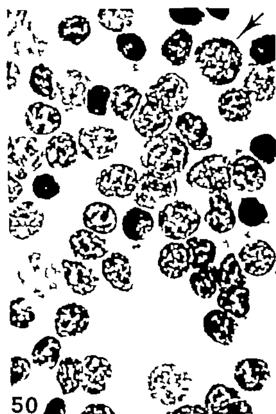
Fig. 50 Lymph node aspirate from LLD-4 (865/67) Blast cells (arrow) and lymphocytes with varying maturity and atypia

Fig. 51 LLD-4 of large cell type (case 1047/63) Mitotic figure in centre x 450

Fig. 52 High power view of field in fig. 51 Atypical lymphocytes and occasional blasts (arrow) x 1120



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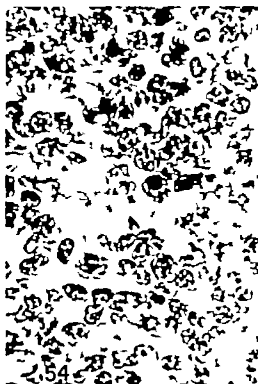
Fig. 53 LLN Lymph node biopsy specimen from case 300/65 Many well-formed, follicle-like structures Towards bottom of illustration a field of more diffuse tumour growth. x 30

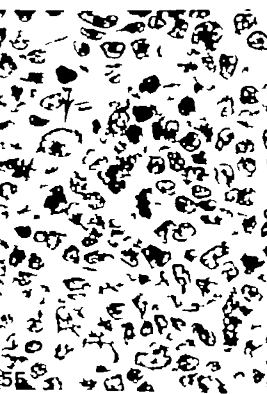
Fig. 54 LLN High magnification of a follicle in fig. 53 Atypical lymphocytes and few blasts. x 1120

Fig. 55 LLN Lymph node biopsy specimen from case 219/73 Field with many blasts (arrows) Mitotic figure in blast (centre) x 1120

Fig. 56 LLN Aspirate from the node illustrated in fig. 55


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Fig. 57 LLN with transition to LLD-4 Lymph node biopsy specimen from case 341/71 x 70

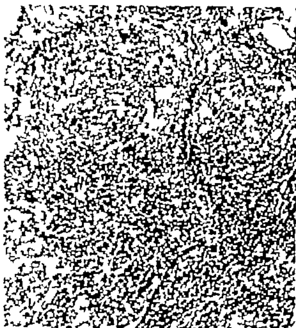
Fig. 58 LLN Higher magnification of fig. 57 Especially in diffuse parts blast cells may be very few and atypia of the lymphocytes need not be striking. x 1120

Fig. 59 LLN Blood picture in case 300/65 demonstrating small and predominantly mature cells but with atypical ("notched ") nuclei A nucleolus occasionally discernible

Figs 60 63 LLN Cells from bone marrow smear of case 219/73 "Notched cells in figs 62 and 63 but immature cells also present.

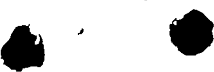
Fig. 64 LLD-4 Bone marrow smear from case 397/59 demonstrating group of rather undifferentiated tumour cells similar to blastic leukemia. Cells with a lymphocytic character are also seen.

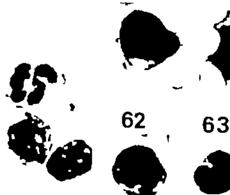
Fig. 65 Blood picture in case 397/59 (compare fig. 64) Apparently mature but atypical cells.





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Fig 66 LLN Bone marrow smear of case 799/73 demonstrating diplococcoid" cells. The cell to the right has immature features.

Fig. 67 Blood picture in case 799/73 Compare figs. 66 and 70 Except for the double nucleus the appearance of the lymphocyte is not strikingly abnormal.

Fig. 68 Lymph node of case 799/73 demonstrating LLN with transition to HL. x 30

Fig. 69 LLN Case 799/73 A tumour nodule Pronounced autolysis but still many cells with double nuclei are visible Some of the blast cells also appear to have double nuclei (arrows) x 1120

Fig. 70 Extra nodular lymphomatous parenchyma of the same node as fig. 69 Many small mature "diplococcoid" cells. x 1120

Fig. 71 HL-cells with double nuclei from focus in fig. 68 x 1120

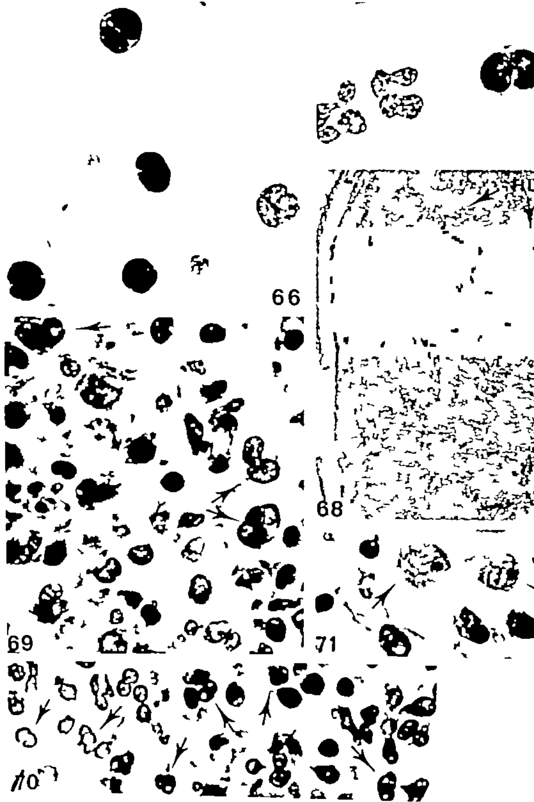

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Fig. 72 Blood smear from case 437/67 (bone marrow group 1 3) Many irregular nuclei.

Fig. 73 Bone marrow smear from case 437/67 (bone marrow group 1 3) Atypical cells some with discernible nucleoli.

Fig 74 Fine needle aspirate of pharyngeal tumour (HL) of case 437/67 Many hyaline inclusions in the cytoplasm.

Fig. 75 Histologic section of biopsy from pharyngeal tumour (HL) in case 437/67 Tumour cells have giant nucleoli. Some hyaline inclusions (arrows) Epithelium in upper right corner Toluidine blue x 1120


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Fig 76 Electron micrograph of pharyngeal tumour of case 437/67 (compare fig 75) Light and dark cells. Hyaline inclusions in cytoplasm of some light cells (arrows) x 4500

Fig 77 Electron micrograph of a dark cell of pharyngeal tumour case 437/67 The cell has a huge nucleolus. Cytoplasm shows many profiles of granular endoplasmic reticulum The cell has plasmacytoid features. x 6000

Fig. 78 Higher magnification of granular endoplasmic reticulum of a dark cell in HL-tumour in case 437/67 In some places electron dense material is accumulated within the granular endoplasmic reticulum similar to what may be seen in plasma cells. x 17000

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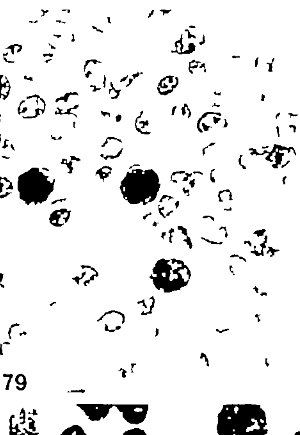


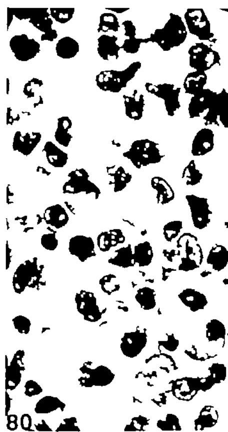
Fig 79 Necropsy specimen of pharyngeal tumour from case 437/67 Many PAS-positive hyaline inclusions in tumour cells Nucleus often pushed to periphery Cell with phagocytosis (lower centre) This cell is probably a reactive macrophage PAS x 1120

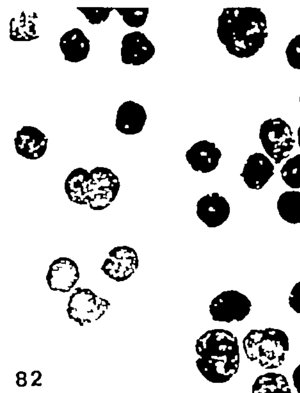
Fig. 80 Same tissue as in fig. 79 stained according to Ladewig In some cells the hyaline inclusions stain red (low centre) in others the inclusions stain light bluish (upper right) The cell in the lower right part of the reproduction contains both red and bluish inclusions Ladewig, x 1120

Fig. 81 Bone marrow smear from case 913/72 (bone marrow group 1 3) All the cells are atypical and a nucleolus is discernible in most of them. Still two generations seem to be recognizable and the cell in the upper left part of the picture resembles a prolymphocyte

Fig. 82. Bone marrow smear from case 109/67 (bone marrow group 1 3) Generally irregular and atypical cells, but few with immature features. Especially the larger cells have cleft nuclei.


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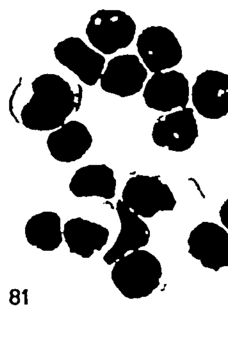

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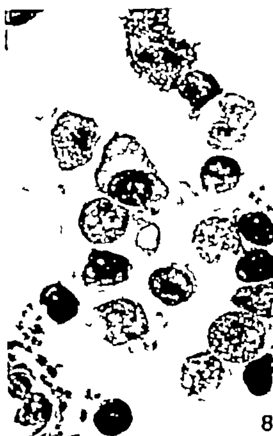
Fig. 83 Bone marrow smear from a case of Waldenström s macroglobulinemia (820/70) A group of cells with a histiocyte lymphocytes, plasma cells, and "lymphoplasmacytoid cells with intermediate morphology Note angular plasma cells.

Fig. 84 Another group of cells in a bone marrow smear of case 820/70 similar to that in fig. 83 Note vacuole in cytoplasm of cell in the centre

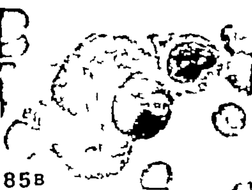
Fig. 85 Plasma cells in bone marrow smear of case 820/70 (macroglobulinemia) with intranuclear "vacuole" Sometimes it is possible to see the vacuole" opening into the perinuclear space and it is really an invagination into the nucleus (fig. 85 B)

Fig 86 Histologic section of bone marrow in Waldenström s macroglobulinemia (case 1224/70) Moderately dense infiltration with lymphocytes and plasmacytoid cells. PAS-positive intracytoplasmic inclusions (arrow) PAS x 370


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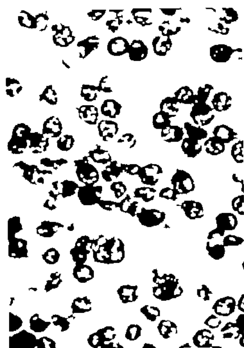
Fig. 87 Lymph node from case of Waldenström's macroglobulinemia (1224/70) Diffusely outlined fields of fairly large plasmacytoid cells (right centre) and smaller lymphocytic cells. x 220

Fig 88 Lymph node in Waldenström's macroglobulinemia (case 1224/70) Mature lymphocytes and some immature cells with irregular nuclei. x 1120

Fig. 89 Dense infiltration of perinodal adipose tissue in Waldenström's macroglobulinemia (case 225/61) Lobular architecture of the adipose tissue is accentuated. x 40

Fig. 90 Waldenström's macroglobulinemia. Another field of perinodal fat tissue from case 225/61 showing accentuated lobulation of infiltrated tissue due to pronounced dilatation of lymphatic vessels. x 40



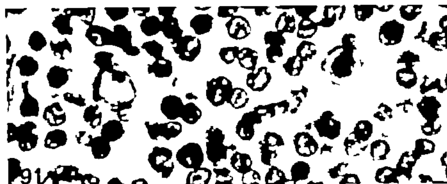


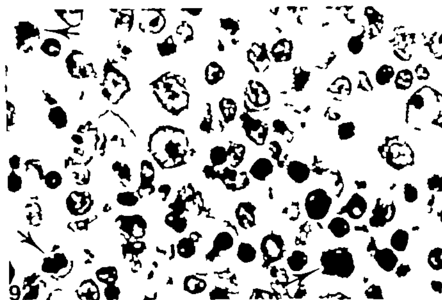

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Fig. 91 Lymph node biopsy specimen from case 1224/70 (Waldenström's macroglobulinemia) Immature cells similar to IF-cells of LLD-1 Mitotic figure in cell to the right x 1120

Figs. 92 and 93 HL-tumour of the spleen in case 1224/70 Many immature cells similar to those of the diffuse proliferation (compare fig. 91) Bizarre tumour cell in fig. 93 Many mitotic figures (arrows) Giemsa, x 1120


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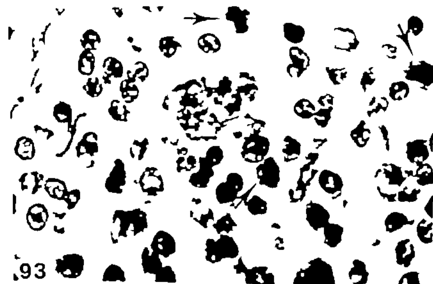

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Fig. 94 Bone marrow infiltrates in case V 434/71 (Waldenström s macroglobulinemia) In the centre of the focus small lymphocytic cells (upper right) surrounded by a brim of larger plasmacytic cells. x 220

Fig. 95 Lung tumour from case V 434/71 Diffusely outlined fields of small lymphocytic cells (left) and larger plasmacytoid forms (right) x 220





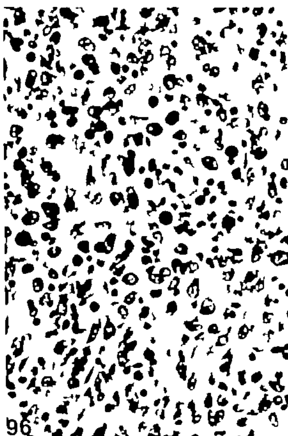
Fig 96 HL from case 777/68 (Waldenström s macroglobulinemia) Section of inguinal lymph node showing polymorphous infiltrates. x 450

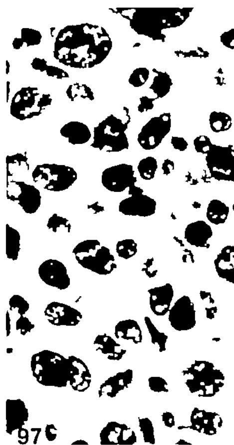
Fig. 97 Higher magnification of fig. 96 x 1120

Fig. 98 Bone marrow smear from the time of the diagnosis of case 777/68 (Waldenström s macroglobulinemia) demonstrating classical picture

Fig. 99 Section of femoral bone marrow obtained at necropsy of case 777/68 Same cytologic picture as that in fig. 98 Compare picture to HL-tumour of figs. 96 and 97 x 450

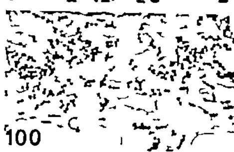
Fig. 100 Amyloidosis of cellular infiltrate in case 777/68 Amyloid rings surrounding fat cells and lump of amyloid surrounded by giant cell Congo red x 250


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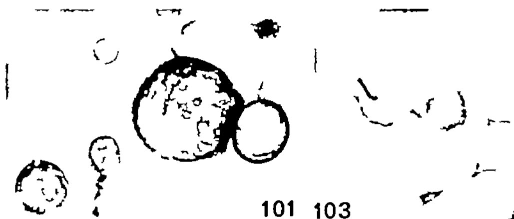
Figs. 101 and 102 Bone marrow smear from case 99/62 (macroglobulinemia) Varying size of tumour cells. Some are very large and plasmacytoid Most cells contain intranuclear inclusions.

Fig. 103 PAS-staining of bone marrow smear of case 99/62 showing heavy staining of background film and of intranuclear inclusions. No nuclear counter stain

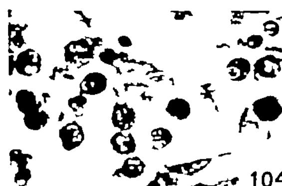
Fig. 104 Section of bone marrow obtained at necropsy of case 99/62 Many intranuclear inclusions in most of the abnormal cells. PAS x 1120

Fig. 105 Bone marrow smear from case 413/61 (bone marrow group 3) The cells are difficult to classify Some resemblance to the smear from cases of macroglobulinemia (see for example figs. 83 84 and 98) However no obvious plasmacytoid cells

Fig. 106 LLD-1 + 2 Mediastinal lymph node at necropsy of case 1095/62 demonstrating diffuse mixture of small lymphocytes and immature cells. The picture resembles LLD-2 x 450


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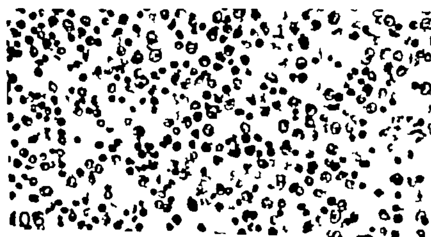

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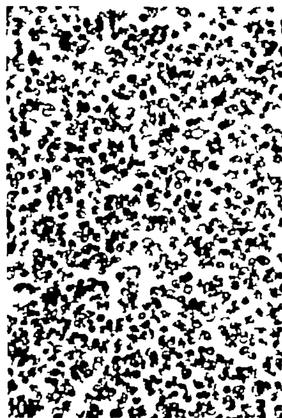
Fig. 107 Tumour of stomach wall of case 737/69 (LLN) In this field many blast cells but no signs of HL. x 450

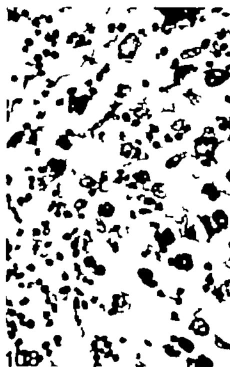
Fig. 108 Splenic tumour in case 737/69 demonstrating nodular HL. Compare fig 107 x 450

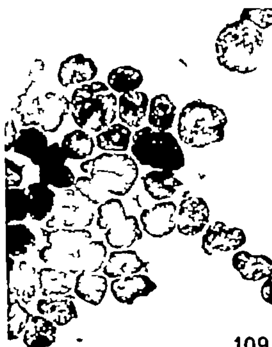
Fig. 109 Bone marrow smear from case 633/68 Necropsy specimens of lymph nodes obtained shortly after this bone marrow smear showed picture of undifferentiated malignant lymphoma Many blast cells in this field but also many atypical lymphocytic cells.

Fig. 110 Bone marrow smear of case 878/64 The picture resembles blastic leukemia This patient had already 50 months earlier the picture of undifferentiated malignant lymphoma in a mediastinal tumour By that time appearance of the bone marrow was normal

Fig. 111 Blood picture in terminal phase of case 878/64 demonstrating cells of lymphocytic size but atypical and sometimes with immature nuclear structure Compare fig 110


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Fig. 112 LLD-I Lymph node obtained at necropsy of case 98/58 showing IF-n At this magnification the foci are identical to the IF of biopsy specimens, but they are often better demarcated x 25

Fig. 113 Higher magnification of node in fig 112 showing 2 prominent IF-n separated by a field of mature lymphocytes. x 170

Fig. 114 High magnification of IF-n Cells are similar to those of IF in biopsy specimens (compare with fig. 2) There are however many atypical cells with irregular and hyperchromatic nuclei and recognition of the different generations is not so easy as in the more orderly picture of the IF of biopsy specimens Atypical mitotic figure at arrow x 670

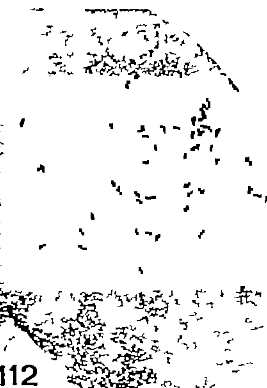

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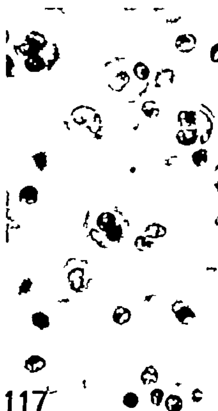


Fig 115 Hepatic focus of Hodgkin s disease in case 31/67 (LLD-1) Necrosis in the centre in the periphery a brim of lymphocytic infiltra tion, in between a polymorphous granulation tissue x 90

Fig. 116 Higher magnification of fig 115 Picture is characteristic of Hodgkin s disease with many multinucleated Reed-Sternberg cells and fibrosis. x 450

Fig. 117 Another part of the field in fig. 115 Many macrophages with phagocytosis of lymphocytes. x 1120


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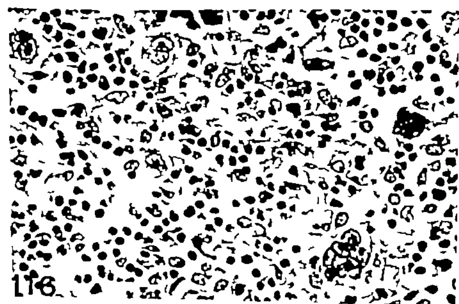
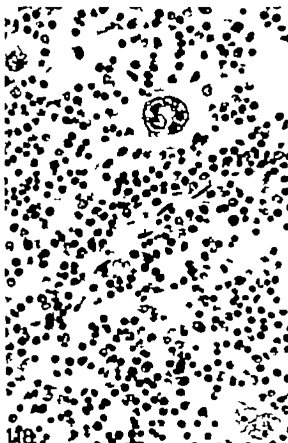

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Fig. 118 Splenic focus of Hodgkin s disease in case 692/66 (LLD-1) Reed Sternberg cells and macrophages and many prolymphocytes x 450

Fig. 119 Hepatic foci of Hodgkin's disease in case 692/66 Many large tumour nodules partly confluent with destruction of liver parenchyma x 30

Fig. 120 Reed-Sternberg cell in smear of lymph node aspirate from a patient with CLL of 4 years standing. The patient was taken ill with a febrile disease after having been in good clinical condition for several years. The nodes grew rapidly The patient died within a short time Case not part of this study x 1300


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Fig 121 Case 1298/65 (LLD-1) Coalescent periportal lymphocytic infiltrates with central foci of HL x 70

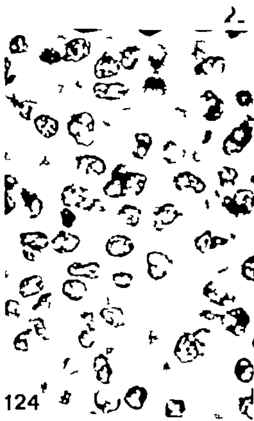
Fig. 122 Higher magnification of fig 121 Note lymphocytic brim around HL tissue x 180

Fig 123 Higher magnification of fig. 122. Note rather abrupt transition between lymphocytic and histiocytic parts x 450

Fig. 124 Higher magnification of HL-tissue in fig. 123 x 1120






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Fig. 125 Case 1298/65 (LLD-1) Coalescent IF-n with transition to HL (lower part) in a lymph node x 20

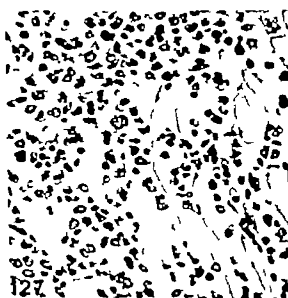
Fig. 126 HL in stomach wall of case 83/64 (LLD 1) Mucosal surface at top x 20

Fig. 127 HL of case 831/70 (LLD-1) Polymorphous tumour tissue infiltrating muscle of thoracic wall x 420

Fig. 128 Higher magnification of fig. 127 Note mixture of lymphocytes and HL-cells x 1120


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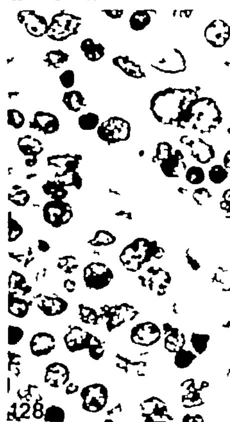
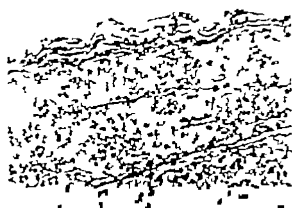

128

Fig. 129 Lymph node of case 42/65 (LLD-1) Marginal sinus filled with polymorphous histiocyte-like cells. Similar cells spread along the sinus within the parenchyma. Toluidine blue x 180

Fig. 130 Focus of HL within the parenchyma of the node in fig. 129 Toluidine blue x 1120

Fig. 131 High power view of cells within sinus of the node in fig 129 Note seeming association of cells with reticulum fibres Toluidine blue x 1120


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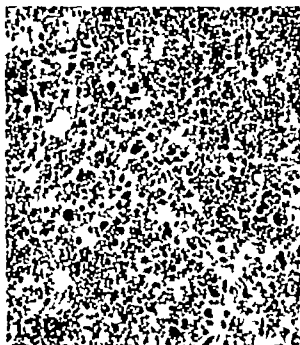

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Fig. 132. Hepatic nodule of HL in case 42/65 (LLD-1) Very polymorphous tumour tissue mixed with lymphocytes. x 180

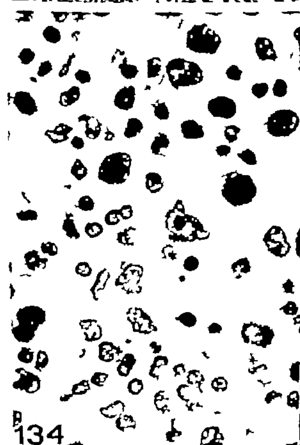
Fig. 133 Lung infiltrate of case 42/65 (LLD-1) Lymphocytic infiltration of interstitial tissue with atypical cells, also seen within the alveoli. x 150

Fig. 134 HL in lymph node of case 1434/64 (LLD 1) Predominantly immunoblastic type Two mitotic figures in the field x 1120

Fig. 135 HL in lymph node of case 136/58 (LLD-1) The cells are very "histiocytic" in appearance Mitotic figure below centre x 450


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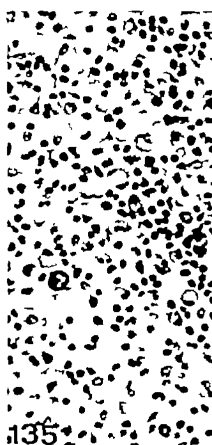
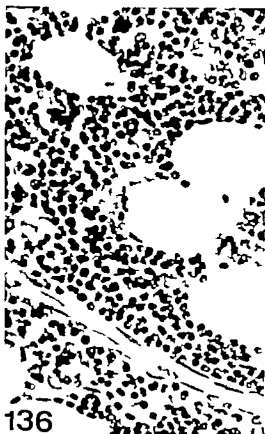

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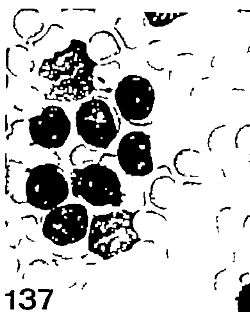
Fig 136 Case 961/61 (LLD-1) Necropsy specimen of femoral bone marrow showing lymphocytic infiltration. x 450

Fig. 137 Appearance of bone marrow smear at the time of the diagnosis of case 961/61 Cytological picture in fig. 136 unchanged

Fig. 138 Lymph node from case 961/61 Transitional zone between lymphocytic infiltration and HL, demonstrating many connective tissue fibres. van Gieson x 160

Fig. 139 HL in lymph node of case 961/61 Fascicular growth van Gieson x 70


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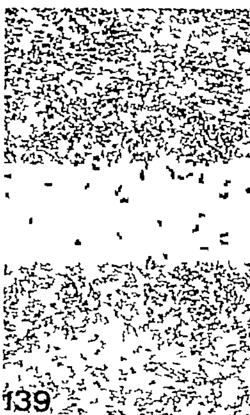
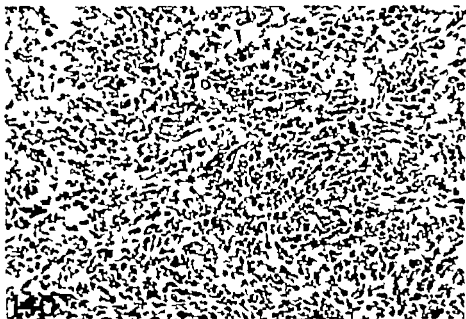
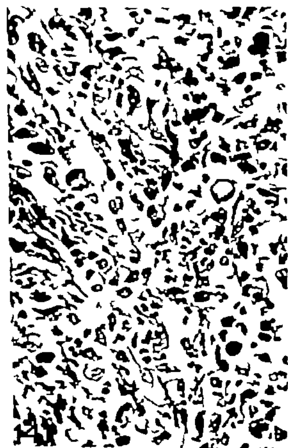

139

Fig. 140 Higher magnification of fig. 139 x 180

Fig. 141 Higher magnification of fig. 140 x 450

Fig 142 Higher magnification of fig 141 Spindle-shaped tumour cells and many plasmacytoid forms Compare cytological picture to that of bone marrow figs 136 and 137 x 1120


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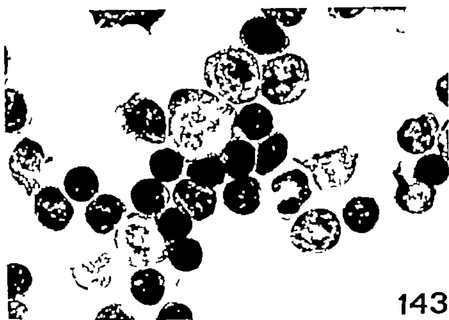

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Fig 143 Bone marrow smear from late phase of case 669/73 (LLD-1) Many lymphocytes, some prolymphocytes, and one large immature cell possibly IF 2 cell.

Fig. 144 Gingival HL-tumour of case 669/73 (LLD-1) Mainly immunoblastic type with prominent nucleoli. Mitotic figure in lower part of picture Toluidine blue x 1120

Fig 145 Appearance of HL tissue in necropsy specimen from the liver of case 669/73 Nucleoli less prominent in autolysed tissue. Cells appear more polymorphous than in fig 144 Many mitotic figures. x 1120


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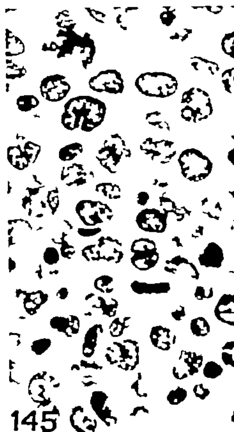
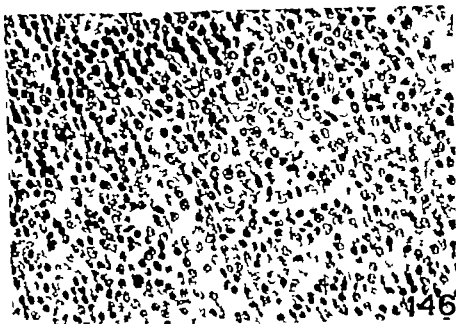
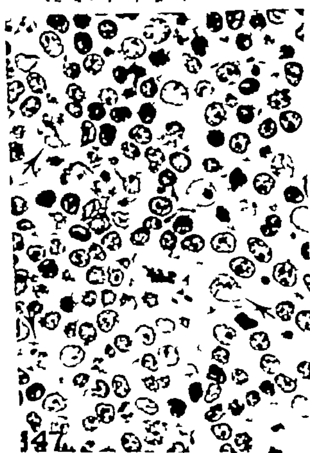

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Fig. 146 Lymph node biopsy of case 829/69 (LLD-1) Transition from lymphocytic tissue (upper left) to confluent IF forming brim around HL focus (not seen in this picture) x 450

Fig 147 High power view of zone with coalescent IF in lymph node biopsy specimen from case 829/69 Occasional cells difficult to assign to any of the IF-cell categories described in the text. Such cells as are seen at arrows have atypia which may correspond to that seen in IF of necropsy specimens. Toluidine blue x 1120

Fig. 148 Very small collection of immature cells in lymph node biopsy specimen from case 829/69 This appearance probably represents the initial phase of an IF The two large cells in the upper part of the picture probably represent telophase of an IF 1 mitosis. In lower left part of the picture some IF 2 cells. Arrows point to some prolymphocytes. Small venule in upper part of the picture Toluidine blue x 1120


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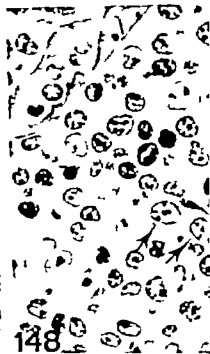
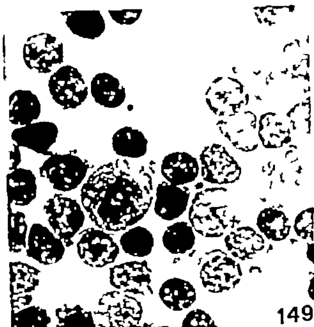

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Fig 149 Lymph node aspirate of a node not affected by HL in case 829/69 (LLD-1) Compare with fig. 153

Fig 150 Electron micrograph of the node illustrated in fig. 149 Some pro-lymphocytes are seen and part of 2 IF 2 cells (left and top right) Note many peculiar densities at contact points (arrows) Some seem to be situated within the cytoplasm depending on invaginations of cell surface x 8000

Fig. 151 Higher magnification of structure seen in fig 150 The cells have interwoven processes with collection of dense material in cytoplasm Inter cellular space bridged by paired spicules within this zone x 60,000





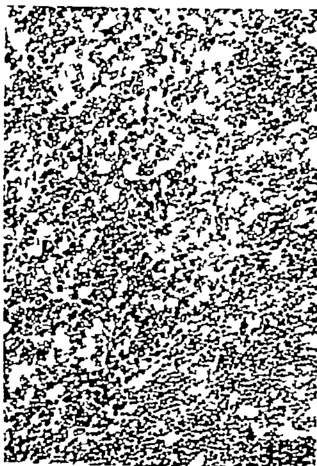
150

Fig. 152 Lymph node biopsy specimen from case 829/69 Transition between zone of coalescent IF (lower right) and HL. Light spaces between HL-cells represent macrophages. x 180

Fig 153 Fine-needle aspirate from node illustrated in fig. 152 Large immature cell probably HL-cell. The majority of cells are lymphocytes and prolymphocytes. Compare fig. 149

Fig. 154 High power view of HL tissue illustrated in fig. 152 Many cells have markedly plasmacytoid features (arrows) Toluidine blue x 1120

Fig. 155 HL tissue in lymph node biopsy in case 829/69 Dead tumour cells are phagocytised within macrophages. Seeming dense intranuclear inclusion body in one of the cells. Such inclusion bodies were often seen and electron microscopically they consisted of granular or structureless detritus. Virus like particles were never seen in them Toluidine blue x 1120


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Fig. 156 Electron micrograph of tumour seen in fig 152 At the bottom of the field a dead cell being phagocytised The other cells in the field are vital tumour cells. The nuclei have some general resemblance to those of IF-cells but are larger and more irregular x 5500

Fig. 157 Nucleus of HL-cell of case 829/69 Two nuclear lobes are connected by a thin bridge Many nuclear pockets x 55,000

Fig. 158 Higher magnification of HL-tumour of case 829/69 Cell in lower right part of the picture is practically identical with IF 2 cell. The other cells in the field are larger and have irregular nuclear contour Note large amount of granular endoplasmic reticulum x 7000





158

Fig 159 Mitotic figure in tumour cell of HL in case 829/69 The cell is closely associated with extracellular material of moderate electron density in lower part of the picture This material is similar to reticulin but could not be demonstrated in the light microscope by silver impregnation x 5700

Fig 160 Heavily contrasted field of HL-tumour of case 829/69 Electron dense material surrounding individual tumour cells and their processes. Within the amorphous material collagen-like fibrils are embedded x 8400.

Fig 161 Hyaline PAS-positive cytoplasmic inclusion in lymphocytic cell of lymph node biopsy of case 258/68 (LLD-I) This cell was found in the 3rd section after a search in two negative sections A rough estimation of the number of negative cells examined before a positive cell was found amounts to 200 000 PAS x 1120

Fig. 162 Same section as fig. 161 One PAS-positive intranuclear inclusion was also found in this section PAS x 1120

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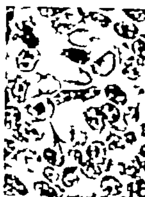
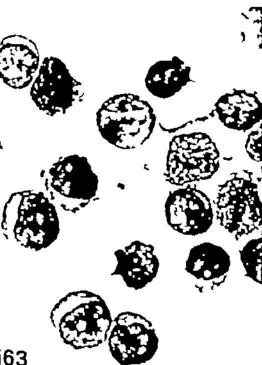


Fig. 163 Bone marrow picture in case 655/63 (LLD-2) at time of the diagnosis Many prolymphocytes.

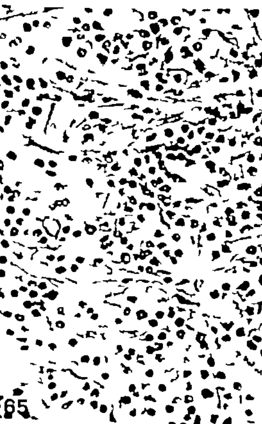
Fig 164 Case 655/63 (LLD 2) Blood picture at time of the diagnosis

Fig 165 Bone marrow picture in necropsy specimen of case 655/63 Fibrosis of stroma with prolymphocytic infiltration x 450

Fig. 166 Border of HL lesion in axillary lymph node of case 655/63 (LLD-2) Prolymphocytes and HL-cell x 1120


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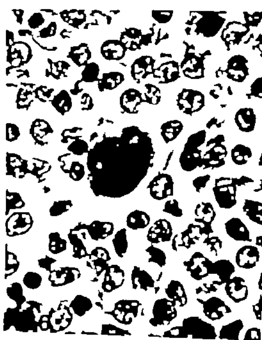
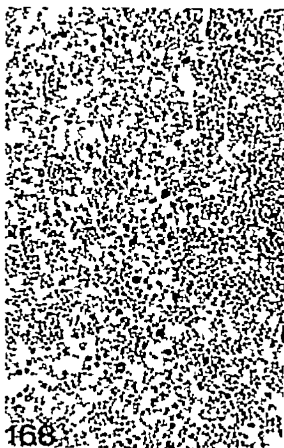


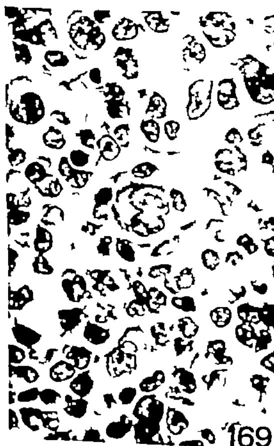
Fig 167 Axillary lymph node of case 655/63 (LLD 2) demonstrating central HL focus compressing surrounding lymphocytic parenchyma x 15

Fig. 168 Higher magnification of HL tissue in fig. 167 x 180

Figs. 169 and 170 High power fields of fig 168 x 1120


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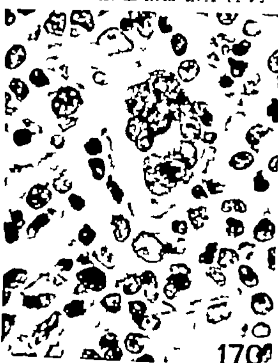

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Fig 171 Lymph node biopsy of case 855/67 (LLD 3) This "cloudiness" is sometimes seen in LLD-3 and may be called nodular according to Rappaport But the tumour nodules do not resemble true follicles Such "cloudiness" has not referred a case to nodular lymphoma in this work. x 35

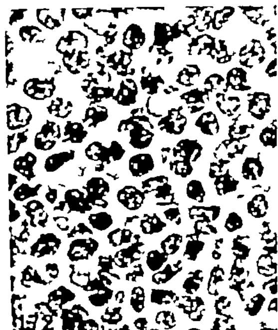
Fig 172 High power view of fig. 171 Predominantly mature lymphocytes, but many atypical x 1120

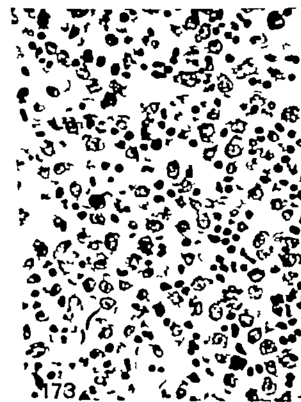
Fig 173 Necropsy specimen from HL tumour in liver from case 855/67 Immunoblastic type of HL, x 450

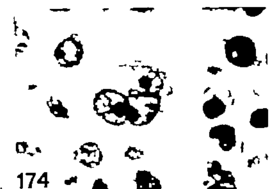
Fig 174 High power view of fig. 173 Multinucleated tumour cell with giant nucleoli somewhat resembling Reed Sternberg cell. x 1120

Fig. 175 Necrotising arteritis in HL tissue from case 855/67 x 170


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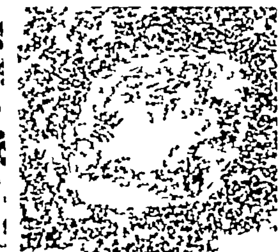

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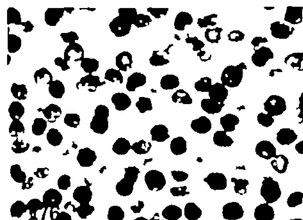
Fig. 176 Case 290/70 (LLD-3) Section of necropsy specimen of bone marrow showing lymphocytic infiltration x 1120

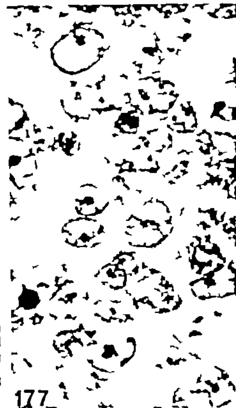
Fig 177 Case 290/70 HL in nasal polyp at time of diagnosis. Compare picture of bone marrow in fig. 176 x 1120

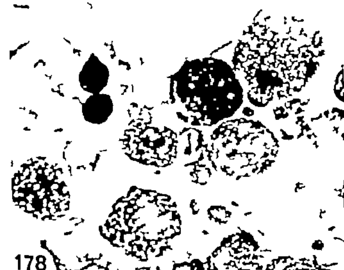
Fig. 178 Case 290/70 Fine-needle aspirate of cervical lymph node affected with same tumour as in fig 177

Fig. 179 Example of HL developing terminally in LLN (case 609/69) The tumour cells resemble those of HL following LLD 1 2 or 3 But the cells are often more variable in size and shape and have smaller nucleoli. But no clear histologic boundaries between the two types. x 1120

Fig. 180 Fine-needle aspirate from lymph node illustrated in fig. 179 The cytologic appearance is very similar to that in fig 178 for example


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Fig. 181 LLD-I Lymph node biopsy of case 2 219 Large, partly coalescent IF This field was selected for electron microscopy x 210

Fig. 182 High power view of large IF IF 1 cell at asterisk. Some IF 2 cells in centre of picture (arrow points to typical example) Arrow is situated on a macrophage whose nucleus is poorly stained with Giemsa A small vessel is seen (top centre) Most of the cells in the field are prolymphocytes. Giemsa x 1300

181

182

Fig. 183 Electron micrograph of IF The large cell in top centre position is a typical IF 2 cell In the right lower corner is a mitotic figure in another IF 2 cell. In the centre of the field some mature lymphocytes. Most other cells in field are prolymphocytes Arrows point to typical examples Reticulum fiber at thick arrow x 3900

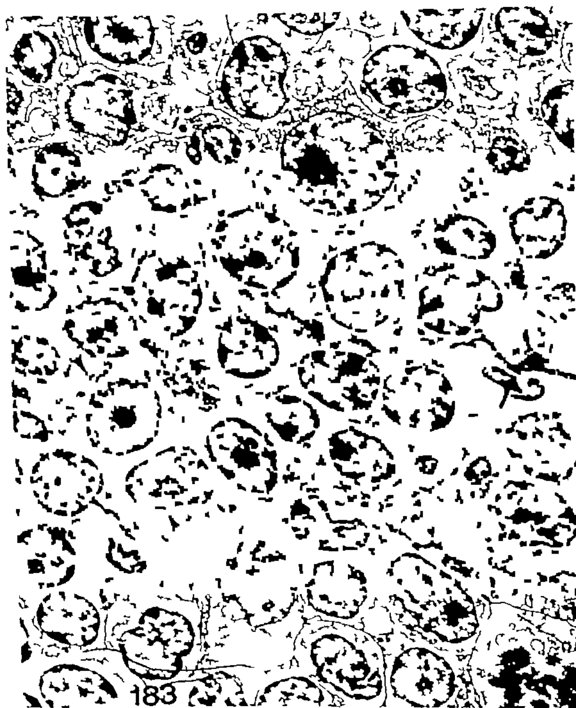

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Fig 184 An IF 2 cell with a tapering process in upper part of the picture (asterisk) A macrophage to the right of this cell. In lower part of reproduction two reticulum cells. They have tortuous processes connected by desmosomes (arrow) x 7000

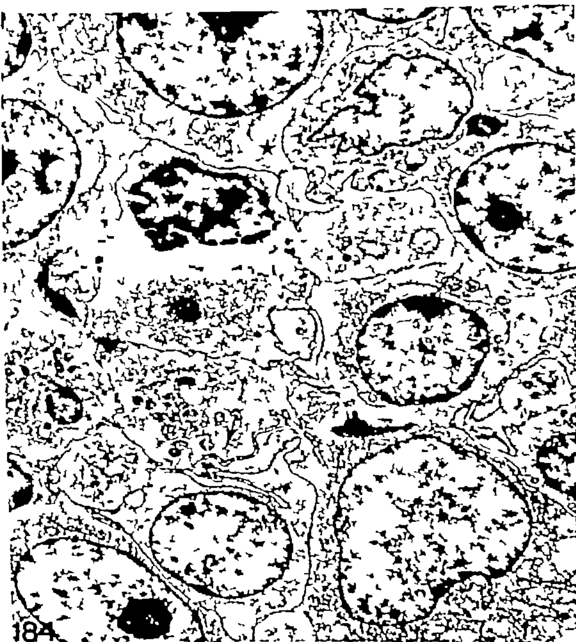

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Fig 185 The process of the IF 2 cell of fig 184 in higher magnification A bundle of tubules at arrow Fine filaments running obliquely to cell surface At tip of the process is a desmosome not ideally oriented to the plane of section Highly complicated surface interrelation of cells. x 46 000

Fig. 186 Higher magnification of connections between reticulum cell processes seen in fig. 184 Two desmosomes. x 25 000

Fig 187 Another cell process with desmosomal connections (this process is seen in the right part of fig 184) It is impossible to know whether such a process stems from a reticulum cell or an IF 2 cell. x 31 000

185

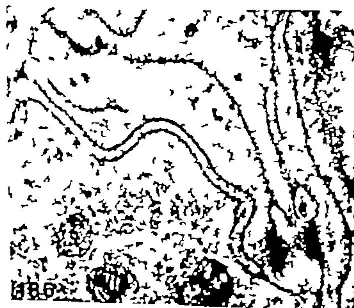




Fig 188 An IF 1 cell. Somewhat irregular nuclear contour many large nucleoli, cytoplasm poor in organelles except for many polyribosomes. x 11 000

Fig 189 A lymphocyte to the left to the right an IF 2 cell with a bifurcated process. This cell is not sectioned through its largest diameter but also at that level the cell was considerably smaller than the IF 1 cell. Compare size of IF 1 cell in fig. 188 (same magnification) x 11 000

188



189

Fig. 190 To the left an IF 1 cell, to the right an IF 2 cell, in the middle an IF 3 cell. Cell sizes not strictly comparable because of sectional effects. The IF 3 cell has a long tapering process towards the right. Many wavy fibrils to the right of the nucleus. Several reticulum fibres. The IF 3 cell shows a desmosome at the arrow (not well visible in this magnification) x 5400

Fig 191 An IF 2 cell to the left an IF 3 cell to the right Note difference in density of cytoplasmic organelles and somewhat different appearance of the granular endoplasmic reticulum. x 12 000

Fig. 192 Elongated cell intimately associated with reticulum fibre The cytoplasm resembles that of IF 3 cells the nucleus has no visible nucleolus in this plane It is not possible to know whether this is an IF 3 cell or a fibroblastic reticulum cell. x 6600

Fig 193 Gall-body like structure in process from IF 3 cell (centre) Similar structures in prolymphocytes to the right and above x 18,500



193

Fig. 194 IF 2 cell in mitosis. Note whorl of granular endoplasmic reticulum Gall-body like granules at arrows. Vacuolisation of mitochondria is due to poor fixation. x 12 500

Fig. 195 A "dark cell" with very long processes, winding in and out of the section. Nucleus in lower left corner winding and branching process arrowed. x 8500

194



Fig 196 Desmosomal connection between two IF-cells. Note the highly winding and complex surface interrelationship between the cells. In many places fine filaments are seen in a peripheral position in the cell, seemingly inserting in the plasma membrane x 30 000

Fig 197 Higher magnification of desmosome in fig. 196 This type of desmosomal attachment was seen most often. A short slightly bent process from a cell has a desmosomal attachment on its side to the body of another cell. Fine filaments seem to insert in the desmosome within the process. These filaments pass for a short distance into the body of the cell. At the origin of the process from the cell body there sometimes appears to be an annular structure Ideally oriented desmosomes were very hard to find while such as had been sectioned at oblique angles were seen more often x 67 500

Fig. 198 Another desmosomal attachment similar to that of fig. 196 x 40 000

Fig. 199 An annular complex of laminated granular endoplasmic reticulum similar to such structures as have been described in leukemic reticuloendotheliosis. Such structures were seen in occasional cells predominantly in prolymphocytes and IF 2 cells. x 30 000

Fig. 200 A macrophage The nucleus is contorted the cytoplasm contains many lysosomal granules of different shape and electron density The cell has a long "tail" x 6000


196


197


198


199


200

Fig. 201 Rare examples of this cell type were found in case 2 219 The cell is ovoid with a smooth outline without interdigitations Parallel stacks of granular endoplasmic reticulum surround nucleus (arrow) The cell is similar to an immature plasma cell. x 10 000

Fig. 202 A prolymphocyte Gall-body like structure at lower arrow Some strands of granular endoplasmic reticulum. Two cross-sectioned reticulum fibres are seen close to the cell (asterisks) They are partly ensheathed by processes of a "dark" cell (arrows) x 11 700

201



Fig. 203 Group of wavy thread like structures in cytoplasm of IF-cell. A membrane bounded body containing polymorphous membraneous material is seen in lower part of the picture x 60 000

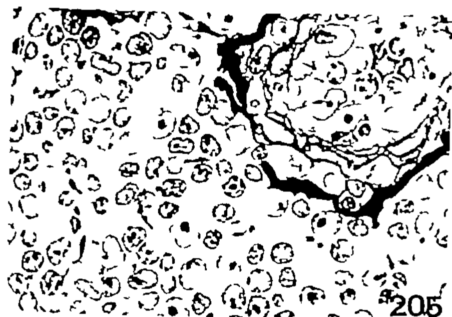
Fig 204 Higher magnification of fig. 203 In the lower part of the picture the structures are cross-sectioned in the upper part they are cut obliquely or along their axis. x 206 000

203

204

Fig. 205 Light microscopical illustration of high endothelium venule within IF The wall consists of many lamellae of basal membrane surrounding pericytes. Lymphocytes are seen traversing the endothelium and within the lamellae of the basal membrane They travel through gaps in the outermost lamella Toluidine blue x 1120

Fig 206 Electron micrograph of lymphocyte (arrow) traversing endothelium of high endothelium venule Another lymphocyte within lumen at top x 12 000



206

Fig 207 High endothelium venule with lymphocyte stagnation. Tendency to development of interlocking processes between the lymphocytes within the lumen. Part of the nucleus of a pericyte in lower left part of the picture (asterisk) To the right of this is a lymphocyte within laminar duplications. Further to the right the cytoplasm of the pericyte is visible again (asterisks) At the uppermost asterisk there is a desmosomal connection between two cells within the basal membrane. A higher magnification of this field is seen in fig. 208 x 7700

Fig. 208 Higher magnification of the field at the upper asterisk in fig. 207 Within a gap in the basal membrane is a desmosome (arrow) In serial sections this appeared to be an attachment point between the pericyte and the IF-cell on the outside of the membrane x 55 000

207



Fig 209 A lymphocyte is seen passing through the thin, innermost lamella of the basal membrane of a venule (the lumen is compressed) On the outside of the membrane the cytoplasm appears clear" and resembles the cytoplasm of the pericytes. x 7500

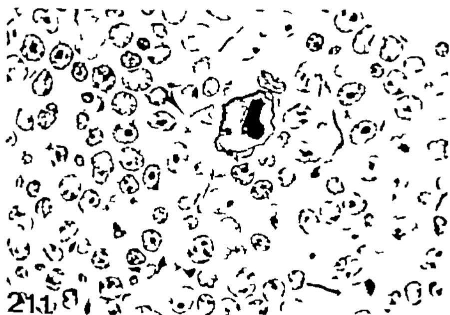
Fig. 210 An immature cell is seen passing the basil membrane of a venule. It has a bud of cytoplasm on the inside of the membrane connected to the cell body through a gap The cytoplasm contains many polyribosomes and the nucleus has several nucleoli. The cell is considerably smaller than a fully developed IF 1 cell (this is approximately the largest diameter of the cell) It might represent a lymphocyte in transformation developing into an IF 1 cell. x 7000

209



Fig 211 The smallest type of vessel seen within the IF It consists of a single row of low endothelial cells and a membrane split into at least two laminae A lymphocyte within the lumen On the outside of the basal membrane a cell with an irregular nucleus (arrow) Light microphotograph. Toluidine blue x 1120

Fig. 212 Electron microphotograph of the same vessel. The laminar duplications enclose a layer of clear cytoplasm belonging to pericytes. The cell on the outside of the vessel has the character of a reticulum cell and contains bundles of filaments (arrow) Its cytoplasm is seen for long stretches along reticulum fibres radiating from the vessel wall On the opposite side of the vessel is a lymphocyte apparently directly adjacent to the basal membrane. x 8100



212

Fig 213 Low power electron micrograph of lymph node biopsy of case 671/66 (LLD-2) The tissue is essentially similar to the IF of LLD-1 x 2000

Fig. 214 Electron micrograph of lymph node biopsy of case 663/58 (LLD-2) The cells of the parenchyma are prolymphocytes identical to those of the IF of LLD-1 A venule is seen with a lymphocyte in transfer through the wall (arrow) x 8000



214

DIAGNOSIS OF CASES REFERRED TO IN TEXT

		Fig.no
198/57	LLD-4	
737/57	LLD-4	
98/58	LLD-1	112 113
136/58	LLD-1 + HL + myeloma	135
663/58	LLD-2	10-16 214
397/59	LLD-4	64-65
690/60	LLD-3	
1120/60	LLD-3 + HL	33-38
225/61	Macroglobulinemia	89 90
413/61	Bone marrow group 3	105
451/61	LLD-4 + HL	40-43
929/61	LLD-2	
961/61	LLD-1 + HL	136-142
1059/61	LLD-4	
99/62	Macroglobulinemia	101 104
535/62	LLD-4	49
1095/62	LLD-1+2	106
185/63	LLD-1	5-6
655/63	Bone marrow group 2 + HL	163-170
1047/63	LLD-4	51-52
1124/63	LLD-1	
83/64	LLD-1 + HL	126
619/64	LLD-4	44
878/64	Undifferentiated lymphoma	110-111
1305/64	LLD-2	
1320/64	Bone marrow group 2	
1434/64	LLD-1 + HL	134
42/65	LLD-1 + HL	129 133
151/65	Bone marrow group 2	18-19
300/65	LLN + HL	53-54 59
600/65	LLD-1	
762/65	LLD-4	
1147/65	LLD-3	26-28
1226/65	Bone marrow group 2	
1298/65	LLD-1 + HL	121 125
613/66	LLN	
671/66	LLD-2	17 213
692/66	LLD-1 + Hodgkin s disease	118-119
963/66	LLD-4	45-48
31/67	LLD-1 + Hodgkin s disease	8-9 115 117
109/67	Bone marrow group 1-3	82

437/67	Bone marrow group 1 3 + HL	72-80
614/67	LLD-1	
855/67	LLD-3 + HL	171 175
865/67	LLD-4	50
1404/67	LLD-1	
258/68	LLD-1	161 162
633/68	Undifferentiated lymphoma	109
663/68	Bone marrow group 2	
777/68	Macroglobulinemia + HL	96-100
1332/68	LLD-1	
204/69	Macroglobulinemia	
609/69	LLN + HL	179-180
737/69	LLN + HL	
829/69	LLD-1 + HL	1-2 146-160
891/69	Macroglobulinemia	
1107/69	LLD-3	
290/70	LLD-3 + HL	176-178
705/70	LLD-3 + HL	20-25
820/70	Macroglobulinemia	83-85
831/70	LLD-1 + HL	127 128
1042/70	LLD-4	
1224/70	Macroglobulinemia + HL	86-88 91-93
341/71	LLN + HL	57 58
V 434/71	Macroglobulinemia	94-95
586/71	LLD-1	
706/71	LLD-4	
902/71	LLD-1	
1029/71	Bone marrow group 1 3	
1140/71	LLD-3 + Hodgkin s disease	29 32
220/72	LLD-3	39
913/72	Bone marrow group 1 3	81
38/73	LLD-1 + HL	
219/73	LLN	55-56 60-63
243/73	LLD-4	
V.251/73	Macroglobulinemia	
272/73	LLN + HL	
352/73	LLD-1	
486/73	LLD-4	
669/73	LLD-1 + HL	143-145
799/73	LLN + HL	66-71
841/73	Undifferentiated lymphoma	
1107/73	LLD-1	
2 219	LLD-1	3-4 181 183-212

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Papers about Long Term
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22 - 24 August 1974

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ACTA MEDICA SCANDINAVICA
SUPPLEMENTUM 595

Review of Papers ab
Long-Term Cardiac Pacing fro
Finland, Norway and Swede
at a Symposium at Öre
22-24 Augusti 1974

Edited by

OLOF EDHAG JØRGEN MEIBOM
and HANS SCHÜLLER

STOCKHOLM 1976

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ACTA MEDICA SCANDINAVICA
SUPPLEMENTUM 596

Review of Papers about Long-Term Cardiac Pacing from Denmark, Finland, Norway and Sweden presented at a Symposium at Örenas 22–24 Augusti 1974

Edited by

OLOF EDHAG JØRGEN MEIBOM
and HANS SCHÜLLER

STOCKHOLM 1976

Tryckeri Balder AB Stockholm 1978

Content

Preface

At the Symposium on cardiac pacing held in Sweden 22—24 August 1974 clinical, therapeutic and technical aspects were discussed.

Artificial pacing of the heart has long been used in the treatment of conduction defects in the Nordic Countries 1) As early as 1958, the first subcutaneous implantation of a pacemaker was carried out on a human being in Stockholm. The patient was in fact the first in the world who had a pacemaker subcutaneously implanted. The pulse generator had been developed by Rune Elmqvist M.D D.E. (Elema-Schönander Co) in collaboration with professor Åke Senning on the staff of the Department of Thoracic Surgery Karolinska Hospital, Stockholm, who placed the epicardial electrodes (Elmqvist and Senning 1959) The patient is doing well 1976 living a normal life and carrying out his profession.

In 1962 transvenous electrodes for long term pacing were used for the first time in Sweden. A majority of patients in the Nordic Countries treated by cardiac pacing, had this type of electrodes inserted after the middle of the 1960 s. The transvenous technique became widely known with the increasing number of reports on the usefulness of these electrodes in long-term pacing (Lagergren et al. 1966)

The development of pacemaker treatment varies in the different Nordic Countries and should be viewed against the differences in geographic conditions and organisatory methods. The pacemaker treatment is carried out at a number of large Pace maker Centers established at certain major hospitals as well as in minor hospitals, admitting only a small number of new patients annually. The construction of the pacemaker and the treatment with a pacemaker require close collaboration at a medical and a technical level. The method of implantation of a pacemaker and routine pulse generator replacement as well as the guidelines for the follow-up of the patients vary in the Nordic Countries. This Symposium was in the first place convened to enable representatives of hospitals, which provide facilities for pacemaker therapy to exchange experiences and to discuss the results achieved concerning technical methods of implantation and the routine follow-up of patients. Another purpose of this Symposium and certainly not the less important one was to bring together physicians and technicians, who are members of the staff of hospitals, with technicians employed by manufacturers of pacemakers. The papers read at the Symposium dealt mainly with the following points surgical technique at electrode implantation, electrode complications, the theoretical background of determination of stimulation threshold, problems related to the generator pocket, failure of the pulse generator control procedures and problems with interference.

Table 1 shows the specialists in the field of

Table 1 Specialists in the Field of Medicine and other Professions represented at the Symposium

	Number
Internists and cardiologists	60
General surgeons and surgeons specialized in Thoracic Surgery	51
Engineers	27
Anaesthetists	8
Clinical physiologists	5
Nurses	5
	136

1) Denmark, Finland, Iceland, Norway and Sweden

medicine together with other professions, which were represented at the Symposium.

The exchange of experiences and ideas between rpresentatives of manufacturers of pacemakers and all those engaged in the care of paced patients is of major importance if cardiac pacing is to be further developed so as to enable to achieve optimum care.

The articles published in this Supplement are revised versions of some of the papers read at the Symposium and were redrafted by the respective authors. The undersigned did in no way alter the factual contents.

The publication of this Supplement would not have been possible without the generous grants of the pacemaker manufacturers Siemens Elema, Sweden, Medtronic Co USA, Cordis Co., USA, and Vitatron Co., The Netherlands, which is gratefully acknowledged.

O Edhag Stockholm · J Meibom Copenhagen · H. Schüller Lund

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Permanent endocardial pacing

An analysis of 90 patients

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ABSTRACT

Primary results and follow up observations in 90 patients with permanent endocardial pacing—covering the period from 1970 to June 1974—are reported. The primary mortality was 3 % (3/90) and late mortality 4 % (4/90) Electrode complications were the most common problem and occurred in 20 % of implantations. Early or late dislocation of the electrode tip was seen in 12 %. With the improved technique it was possible to decrease it significantly through the period The mean battery life time of Siemens-Elema pacemakers was 26 months 10 % of the failed batteries were replaced urgently So far the rather high frequency of electrode complications diminishes the advantages of the pacemaker treatment.

Table I Indications for implantation of permanent pacemaker

Indication		No of patients
Atrioventricular block		71
A—V block III, permanent	41	
A—V block III, permanent, surgical	2	
A—V block III, transitory	23	
A—V block II, transitory	5	
Other indications		16
Bifascicular block (complicated)	6	
Sinus arrest or sinoatrial block	5	
Sinus bradycardia with ventricular tachycardia	3	
Atrial fibrillation with bradycardia	4	
Combination of indications		3
Total		90

The effectiveness of permanent pacing in reducing the mortality of patients with chronic atrioventricular block has been demonstrated in several series (1, 3, 7,9 10) but a certain morbidity rate due to post implantation complications or technical failures still remains. Over the years, technical improvement of the pulse generators has increased the proportion of other faults.

The transvenous electrode technique has been exclusively used in many clinics due to its simplicity We have used it since 1963 Our initial experience has been reported by Inberg et al. (8) Several surgical and other details, however have been altered since then. In this report the effect of these factors on the primary complications and the follow-up is presented.

MATERIAL AND METHODS

From January 1970 to June 1974 a permanent pacemaker implantation was carried out in 90 patients. This series includes 51 men and 39 women. The mean age of the 39 women was 67,8 years, ranging from 11 to 90 years. The mean age of the 51 men was 65,3 years, ranging from 32 to 85 years, and for all the series 67 years, ranging from 11 to 90 years. During the same period, 73 battery changes were performed. It was thus possible—totally or partially—to follow up 163 pulse generators. The indications for pacemaker implantation are shown in Table I. Congestive

Table II Mortality after permanent pacing

Primary mortality 3 patients	(3 %)
1 massive pulmonary embolism	
1 recidive myocardial infarction	
1 myocardial infarction	
Late mortality 4 patients	(4 %)
1 myocardial infarct	
1 myocardial failure	
1 staphylococcal sepsis	
1 unknown (technical failure?)	
Total mortality 7 patients	(7 %)

heart failure before implantation of the pacemaker occurred in 26 patients (29 %) and an Adams-Stokes syncope in 46 patients (51 %). A fixed rate pacemaker was used in 31 patients and a QRS-synchronous one in 57 patients. An atrial triggered unit was used only twice. Siemens Elema pacemaker (EM 152, EM 153, EM 155, EM 156) was used in 81 patients and Medtronic pacemakers (5870, 5862) in 9 patients. Siemens-Elema endocardial electrode (EMT 588 B) was exclusively used. The electrode was inserted through the external jugular vein under local anaesthesia and its position was checked by fluoroscopy. Only exceptionally was the internal jugular vein used. General anaesthesia was used only on children and in those cases where a mediastinoscopy for the atrial detective electrode was needed. Since 1972, a measurement of the stimulation threshold was used in addition to fluoroscopy, a subcutaneous pacemaker pocket (without drainage) in the upper left abdomen replaced the use of a rectus sheath (also without drainage) and the prophylactic use of antibiotics was stopped.

After the primary postimplantation check, the next check was one month later and then after every third month. 0 months after implantation the intervals between successive checks were one to two months. In addition to the clinical, ECG and chest X-ray control, phonoanalysis of pacemaker impulse was performed (4, 8). Criteria for pacemaker change were: following change ... 5 impulses/min, impulse ... change ... fall in maximum amplitude ... % and ... ratio

Table III Follow up and survival rate after start of permanent pacing

Time	1 month	1 year	2 years	3 years	4 years
Followed up	90	67	43	23	12
Survived	87	65	41	22	12

change 20 % as compared to the data one month after implantation.

CLINICAL RESULTS

Survival and mortality

The mortality rate after pacemaker treatment is seen in Table II. Primary mortality (30 days) was 3 % (2 myocardial infarcts and one massive pulmonary embolism, all confirmed at autopsy). Four patients died during the follow up period, one of them of staphylococcal sepsis after recurrent infections around the electrode wire in the neck and battery pocket.

82 out of 90 patients are still alive. The survival/follow up data are presented in Table III.

Electrode complications

These complications and their treatment are shown in Table IV. Early or late dislocation of the electrode occurred in 11 patients (12 %). The time of dislocation is illustrated in Fig. 1. In six patients the dislocation occurred twice. The treatment consisted of repositioning the electrode in 3 patients, insertion of a new electrode in 5

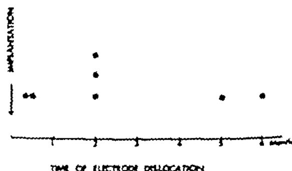


Fig. 1. Time of dislocation of transvenous electrode in 11 patients.

Table II. Electrode complication after endocardial pacing and their management (90 patients)

Complication and treatment	No of patients	
Electrode dislocation	11	(1 %)
Reposition of electrode	3	
Insertion of new electrode	5	
Insertion of epicardial electrode	3	
Infection around electrode	4	(4 %)
Insertion of new electrode	2	
Revision and antibiotics	2	
Increased threshold	3	(3 %)
Insertion of new electrode	1	
High voltage energy source	1	
Glucocorticoid treatment	1	

patients and insertion of a screw-in sutureless myocardial electrode through a substernal incision in 3 patients. One fractured wire was detected of change of decay ratio and repaired.

In 4 patients an infection in the neck surrounding the electrode occurred and was treated by surgical revision and antibiotics in 2 patients and by implantation of a new electrode in the other 2 cases.

The increase in the stimulation threshold, resulting in an exit block, which occurred in 3 patients was successfully treated with prednisone (40 mg daily for 4 weeks) in one case with the insertion of a new electrode without previous cortisone in the second case and with a new high voltage energy source in the third case. The last patient, an 11 year-old girl, got a paediatric pacemaker (4.0 volt) after total block during open heart surgery. An exit block occurred in few days and no electrode dislocation was seen. Prednisone doses of 30 mg daily for two weeks were unsuccessful wherefore the pacemaker pocket was re-opened and a threshold of 3.6 Volt was measured. An adult size fixed rate pacemaker (EM 152 C) was connected and the postimplantation follow up has been uneventful.

Pacemaker pocket complications

A pacemaker pocket manipulation was performed in 163 patients. Two pocket infections occurred,

Table 3. Frequency of some complication with earlier and present technique

Used method and complication	No of patients	
Antibiotic prophylaxis	59	
Infection complication	3	(9 %)
No antibiotic prophylaxis	104	
Infection complication	1	(1 %)
Implantation with fluoroscopy only	33	
Electrode dislocation	6	(18 %)
Fluoroscopy + optimal threshold used	57	
Electrode dislocation	5	(9 %)
Fixation of electrode on jugular vein	55	
Electrode dislocation	7	(13 %)
No fixation of electrode	35	
Electrode dislocation	4	(12 %)

constituting a frequency of 1 %. The treatment consisted of change of pacemaker and of its position. One pacemaker extrusion due to non infective necrosis of the overlying skin was also treated in the same way. One seroma in the pocket was aspirated.

Other complications

These include one primary implantation into the coronary sinus which was corrected by electrode reposition. In one case the extrusion of an indifferent electrode was successfully treated by revision and antibiotics. In a few cases some competitive rhythm with the fixed rate equipment occurred and was usually treated with antiarrhythmic drugs but in one case the change of pacemaker to one of demand type was necessary.

Due to overlapping of the complications in a single patient, the over-all frequency of patients showing some sort of complication was 24 % (22 patients).

Other observations

The pacemaker life time was analyzed in 62 patients in whom the detection of impending or acute energy-source failure led to replacement of the pacemaker. This includes 53 Siemens-Elema units with the mean duration of 26 months (4—

36) and 9 Medtronic units — mean 25 months. Two pacemakers were replaced without signs of impending failure because they exceeded of the maximum expected life time, as reported by the manufactures. These are excluded from the analysis, as are units replaced due to infection, electrode complication or pure exit block. An emergency or semi-emergency replacement was carried out in six patients at 18 22, 29 29 30 and 35 months. In 3 cases the total exhaustion occurred within 4 weeks of the last check. No mortality due to battery failure could be definitely confirmed

The comparison of the frequency of primary complications following the use of past and present techniques is shown in Table V

DISCUSSION

The general acceptance and widespread use of pacemakers as well as improvements in engineering and in surgical techniques make continuous monitoring of results and complications mandatory. There is no doubt, that in large pacemaker clinics treated by experienced staff there is a low rate of surgical complications and the education of staff is more easily organised. The necessary post-graduate training in smaller clinics probably increases the frequency of primary surgical complications. The operations in our small series has been performed by relatively few but changing hands.

The strict indications earlier used by us for long-term pacing (8) have been liberalized. In the former material 94 % of the patients had had Adams Stokes syncope whereas the present figure was 51 %. There has also been a change from fixed rate units towards demand types in the first implantation a fixed rate pacemaker was used in the present series in 31 % of the cases vs 86 % earlier. Sinoatrial rhythm disturbances and recurrent tachycardias in connection with a bradycardia was a new and expanding indication area. This has been a trend in many clinics (–, 15)

Before 1969 when the pacemaker follow up clinic began regular pulse analysis, the rate of battery failure leading to emergency replacement was as high as 64 %. Emergency replacements have now decreased to 10 % corresponding to the follow-up results reported by others (4, 5 11). Recently the failure of all cells within four weeks was seen in three pacemakers after normal running at 28 28 and 34 months. Therefore it seems to us unjustified to run the pacemakers to the extreme limit. The 26 months average life span of Siemens-Elema pacemakers was 10 months more than that reported 5 years ago (8). Similar figures are reported by others (5 12, 13 14, 15)

Careful haemostasis and by using the same shape and form of pacemakers to avoid unnecessary tissue damage and tension has in the present series given a frequency of complications involving the pulse generator pocket of 1 %. No difference was found in complication rate between rectus sheath and subcutaneous battery pockets. We therefore prefer the subcutaneous placement because of its greater simplicity under local anaesthesia.

The primary mortality in our series was 3 % but none of the deaths could be referred to the endocardial technique. The figure in our series is similar with the observation of Serematis et al. (14)

The infections in our series occurred mainly in connection with an electrode repositioning due to catheter tip displacement. There was one death from infection, giving a frequency of 1 %. The collective figures in the literature have been from 0 to 1 7 % (15)

Our discontinuation of antibiotic prophylaxis was not based on empirical findings, but this series distinctly demonstrates that this kind of treatment is unnecessary

At the present time the major source of serious complications in permanent endocardial pacing is the electrode. The displacement of the electrode tip followed by replacement and increased risk of infection, is a well known problem. The rate of electrode complications in our series, 20 % corresponds to figures of Grendahl (6). Therefore before full benefit of the long-term pulse generators can be gained, significant improvements with endocardial electrodes are needed. The value of some new improvements in endocardial electrodes, such as a reduction in the size of the tip to increase current density and collar near the tip to help its

permanent fixation, still waits to be proven in comparative series So far we think the most important field where improvement in long-term endocardial pacing can be done is the careful primary technique to minimize the frequency of still too many electrode complications of which dislocation is the most common drawback.

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Pacemaker wires and electrodes.
A follow-up study

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ABSTRACT

In 362 patients on permanent pacing, follow up with regard to pacemaker electrode function time and connection to pulse-gener tors has been carried out. In 1 patients Elema picardial lectrode were used with an average funct on time of 3.8 years. 32 Elema EMT 588 endoca dial electrodes were used in 216 patients. A erage observation time for the lectrodes was 3.3 years. Sixty-eight lectrodes ha been followed for more than 5 years. Early electrode complications comprise 10 per ent of d splacements befor mplantation of the pulse generator and nother 6 per ent of electrode dis- lacement within the first 3 months after implantation. Flex per cent of the lectrodes had t be corrected due t high th eshold alue before impl ntation and another 6 per ent during the f rst 3 months after implantation of pulse generator.

On hundred nd fifty fiv unipola electrodes of the types Cordis, Medtronic Elem EMT 282, and Stanium were implanted in 149 patients. A erage observ t on time for the electrodes was 1 years. During the first 3 months aft pacemaker implant per ent of the lectrodes were dislocat d, 5 pe ent failed due t high threshold lue. Three perf rations of the ght ent icl occurred, w h- out serious complications. Lat implicat ons after 3 month f r th EMT 588 electrode included 1 per ent lectrode d sl ions 1.5 per ent f 1 due to high threshold, 5 ases of w re break and 4 defects in the insulation. Many of he la electrod omplications w r probably ca d by replacement op ations f pul generators. The most f equent la ompl n f he conventional unipolar lectrod h k wh h oc urred in 5 ses.

Technical improvement n c diac pa g the last few years has mai ly been on pulse genera ors energy sources m and isotope cells have appeared, and the traditional mercury cells have been improved. Some pulse generators hermetically sealed. The internal energy consumption is reduced due to improved circuits. Low energy pacers are available, to be used on small surface electrodes.

As a result of these developments it is expected that the pulse generators we are now using will have an effective life to considerably longer than the average two years of their forerunners from the late 1960 s. Therefore it is reasonable examine the pacemaker wires and electrodes, to see if they possess the durability which the new genera tion of pulse generators requires.

In the present paper a follow up of pacemaker w es and electrodes has been performed.

A follow up study of the patients has previously been published in 1969 (5).

MATERIAL

At this hospital 363 patients have had an implanted permanent pacemaker from August 1961 to 31/12 1974. 281 patients had A V block, 76 patients had S-A block and 8 patients re treated for tachyarrhythmias. One patient, an american tourist who left the country 1 month afte implantation of pacemaker is lost from the follow ud l ded from the material and thus the present based on 362 patient.

METHODS

1 r al lectrodes were sed from August M 1961 A set f 3 lectrodes, one different,

one indifferent, and one spare electrode, was sutured to the pericardium during thoracotomy

Elema endocardial electrodes type EMT 588 were used exclusively from June 1964 to August 1968. From August 1968 to May 1973 we partly used EMT 588 electrodes, partly electrodes with guiding stylet (Cordis Unipolar, Medtronic Unipolar and a few Medtronic bipolar). From May 1973 we used only unipolar electrodes with guiding stylet (Cordis, Medtronic, Elema, Stanium).

The positioning of the EMT 588 electrode was done by different surgeons, under guidance by the cardiologists until 1969. Later on, positioning of electrodes was done by one of the two cardiologists currently responsible for the pacemaker therapy. All operations on pacemaker-pockets were done by surgeons, and under general anesthesia. Until 1970 the right external jugular vein was preferred, and the wire was led behind the clavicle and thence subcutaneously to the abdominal region. After 1970 the cephalic vein was preferred and used in 80 per cent of the cases. In 20 per cent no accessible cephalic vein was found. In 15 per cent an external jugular vein was used. In 5 per cent of the patients the internal jugular vein was used. The pulse generators were placed in the abdominal wall behind the rectus muscle until 1970 and in the thoracic region later on. From July 1973 the wire has been secured outside the vein with a butterfly clamp.

The Elema EMT 588 electrodes were positioned with the patient in left lateral position. A guiding catheter was not used. In the majority of the cases a two stage procedure was followed. In the first operation the electrode was positioned under local anesthesia and the wire taken down subcutaneously to the right groin and connected to an external pacer. In the second operation, one to two weeks later, the pulse generator was implanted in the abdominal wall behind the rectus muscle (2, 3, 8).

The patients have been followed up with regular checks in a pacemaker clinic at the hospital. The checks were performed by the cardiologists who also were responsible for assessing the need for permanent pacing and the placement of electrodes. Photoanalyses with a Philips oscilloscope PM 3 36 has been used during routine checks and in the diagnosis of suspected failures since 1966. An elective policy for replacement of pulse generators was followed until 1971, then for the next two years partly an elective and partly a selective replacement policy was followed.

From June 1973 we have used a strictly selective replacement policy.

Elema epicardial electrodes

These electrodes were used on the first 12 patients treated from 1961 to May 1964. A total of 13 sets of electrodes were implanted. The total observation time for these electrodes was 51 years (average 3.8 years). The end of life point for the calculations was when the last of the 3 electrodes were out of use or the patient died. The reasons for electrodes being out of service are shown in Table I. Four electrodes were out of use due to high pacing threshold, the underlying cause may have been wirebreak, loosening of electrodes from the myocardium or exit block. Two electrodes functioned for 10 and 7 years respectively, the others for less than 5 years. For the 6 patients followed up until death, the average observation time was 4.5 years (0.5—10) and for the 4 patients followed up until pacing failure due to high threshold the average observation time was 3.5 years.

Elema EMT 588 endocardial electrodes

A total of 232 electrodes were used in 216 patients. Total observation time was 791 years, average for each electrode 3.3 years.

In 205 patients a two-step procedure was followed. No major infections were observed in these cases but in a few patients the pulse generator had to be placed in the thoracic region due to local infection in the groin. Prior to implantation of pulse generator 21 electrode corrections (10 per cent) were performed due to high threshold (i.e. pacing threshold higher than about 4 Volt).

Early electrode complications after implantation of pulse generator, i.e. complications during the first 3 months appears from Table II. The cases listed as high threshold represent also loss of capture without visible dislocation on X-ray. A total of 24 re-operations had to be performed (10 per cent). Of 13 dislocated electrodes 12 were corrected and one replaced with a new electrode. Of 10 electrodes with high threshold 6 were corrected. In the one patient who had diaphragmal trigging the electrode was corected.

Late electrode complications, i.e. complications after 3 months are shown in Table III, details about lead breaks and insulation defects in Table IV. One wirebreak was in a special thick version of the lead, later abandoned. One was located in an acute bend of the lead in fibrous tissue near

Table I Major reasons for electrodes being out of service

Electrode type	No used	No used terminated	No still in	Reasons for termination of electrodes								
				Deaths No	High threshold No	Dislocation No	Fracture No	Insulation defect No	Extrusion No	Infection No	Other No	Pacing terminated No
Elema epicardial	13	13	0	6	4	0	0	0	2	0	1	0
Cordis or Medtronic epicardial	3	0	3									
Endocardial electrodes												
Elema EMT 588	232	142	90	107	13	7	1	2	4	1	2	5
Cordis	82	17	65	13	1	0	1	0	0	1	0	1
Medtronic unipolar	49	13	35	10	3	1	0	0	0	0	0	0
Stanicor	15	4	11	2	2	0	0	0	0	0	0	0
Elema EMT 282	9	3	6	2	0	0	0	0	1	0	0	0
Medtronic bipolar	6	3	5	2	1	0	0	0	0	0	0	0
SUM	409	196	213	142	26 (23)	8 (21)	2	2	7	2	5)	4

) two discolorations of wire one damaged during replacement operation.
Figures in brackets indicate complication before pulse generator was connected

the pacer and the third in a peripheral piece of lead distal to a splice. Two defects in insulation were located under tight silk sutures for anchoring of the lead. The sutures seemed to have "melted away" the polyethylene insulation. One defect in the insulation was due to a cut in the lead near the pacer during a replacement operation. The fourth occurred in an electrode introduced through the internal jugular vein, and was probably due to a defect in insulation at the entry of the vein, provoked by an abrupt movement of the right arm. Late exit blocks were associated with high threshold values measured in electrodes without visible damage to the wire or visible electrode dislocation

Table II Endocardial electrode complications during the 3 months after implantation of pulse generator

Type	No of electrodes	Dislocation	High threshold	Perforation	Other
Elema EMT 588	232	13 (6 %)	10 (6 %)	0	1 (0 4 %)
Cordis	8	6 (7 %)	2 (2 %)	2 (2 %)	1 (1 %)
Medtronic unipolar	49	3 (6 %)	3 (6 %)	0	1 (1 %)
Stanicor	15	2 (13 %)	2 (13 %)	1 (8 %)	0
Elema EMT 282		0	0	0	0
Sum Cordis, Medtronic unipolar Stanicor	155	11 (7)	7 (5 %)	3 (2 %)	2 (1 %)
Medtronic bipolar	6	0	1	0	0

) diaphragmal stimulation
) infection

Table III Endocardial electrodes after implantation of pulse generator complications after more than 3 months

Type	No electrodes at risk	Dislocation	High threshold	Break of lead	Defective insulation	Thrombo-embolism	Infection
Elema EMT 588	16	8 (4 0 %)	11 (4 5 %)	3 (1 4 %)	4 (1 8 %)	1 (0 5 %)	1 (0 5 %)
Medtronic bipolar	6	1					
Cordis (2 and 4 mm)	63	0	0	5 (9 3 %)	0	1 (1 5 %)	0
Medtronic 6905 6907	38	0	0	0	0	0	0
Stanicor	10	0	0	0	0	0	0
Elema EMT 282	6	0	0	0	0	0	0

on chest X ray Details of late electrode dislocations and late exit blocks are shown in Table V Of the 8 electrode displacements 2 were clearly related to operations for replacement of pulse generator. Another two were discovered between one and two months after pacer replacement operations in previously stable electrodes, and were probably related to the operations. The other 4 all occurred during the first year after introduction of the electrode. Of the 11 exit blocks 2 came within 2 months after pulse generator replacements, in previously stable electrodes. Another two developed between 11 and 16 months after replacement operations in previously stable electrodes. In these 2 cases reduced amplitude in the skin potentials were also measured, indicating that the exit blocks possibly were related to increased resistance in the electrode system. In one case X ray examination of the heart indicated a possible epicardial position of the electrode due to penetration of the right ventricle Six cases of exit blocks occurred during the first 15 months after positioning of the electrodes, three in electrodes previously corrected and one in an electrode with a lead splice One of these electrodes was repositioned and functioned for another 2½ years until the patient died of an unrelated cause.

Pulmonary emboli has been observed in 4 patients. One had a thrombus in the superior vena cava verified by angiography In 2 the origin of the embolus was not verified and the fourth died from post operative embolus after a pacemaker replacement operation. At autopsy small thrombi have been observed on the pacemaker electrode in 2 cases. Infection propagating from the pacemaker pocket and a secondary deep venous thrombosis was seen in one case, one year after implantation of the pacemaker The electrode was removed and the patient was given a Medtronic epicardial "screw in" electrode. At autopsy one electrode was found in a coronary vein near the apex region where it had been functioning adequately for one year until the patient died of unrelated causes. Persistent fistulae from pacing wires were seen in 7 patients. In 4 of these the wires were not in use In some additional cases fistulae from wires have been corrected with local operations.

Of 232 electrodes used, 90 are still in function. Reasons for electrodes being out of function appears in Table I A hundred and seven electrodes are non functioning because the patients died. Twenty of these were sudden deaths. The number of electrodes in function related to the year of implantation appears from Table VI. Of 86 electrodes introduced in 1964 to 1967 24 (35 per cent) are still in function. Three corrective operations had been done on these electrodes. The incidence of failures in pacemaker electrodes related to observation time is shown in Table VII. The incidence of failures in wire and electrode is not high, and seems not to be related to the function time of the electrodes. Sixty-eight electrodes have been followed for more than 5 years and five for more than 9 years.

Splicing of Elema EMT 588 wires has been done with a special connector (EMT 544) in 16 wires. Total observation time for the splices is 37 years, average 2.3 years. One of the splices failed due

Table V Elema EMT 588 electrodes: late dislocations and exit block ... perfied

	Electrode life (months)	Interval after last pacer replacement (months)	Action	Remark
Dislocation	12	0	New electrode	Occurred during pacer replacement operation
	72	6	New electrode	Too tight after pacer replacement operation
	33	1	New electrode	
	48	33	New electrode	
	12	12	New electrode	
	9	9	New electrode	Dislocated after 1 month, corrected
	4	4	Corrected	
	4	4	Corrected	
Exit block	60	2	New electrode	
	24	2	New electrode	
	72	11	New electrode	Also reduced amplitude in skin potentials
	60	16	New electrode	Also reduced amplitude in skin potentials
	31	27	New electrode	Epicardial position
	15	15	New electrode	T [illegible] months after blind correction
	12	12	New electrode	Wire spliced previously
	9	9	New electrode	
	6	6	New electrode	Early dislocation corrected
	6	6	New electrode	Early exit block corrected
	6	6	Corrected	

to current leak which occurred after 5 years, another electrode with splice had to be replaced due to exit block one year after the splice.

Unipolar endocardial electrodes with guiding stylet

One hundred and fifty five unipolar endocardial electrodes with guiding stylet have been used in 149 patients. Of these were 76 Cordis 4 or 2 mm tip, 6 Cordis ball tip, 47 Medtronic type 6905 or 6907, 2 Medtronic type 6909 (without flange), 15 Stanium 4 or 2 mm tip and 9 Elema EMT 282. Total observation time was 190 years, average 1.2 years. Only 6 patients have been observed more than 4 years. Twentyseven patients died after an average observation time of 0.9 years. Electrode complications during the first 3 months are shown in Table II. Of the 11 electrode dislocations 10 were [illegible] corrected and one repl[illegible] 7 electrodes with high threshold [illegible] [illegible]ted and

Tal l 3 I Follow p f El m EMT 589 pac m ker electrod

Y of introduction	N of lectrodes	No lectrodes still in function	Causes for electrodes out of function		
			Deaths no	F dures in wire or electrode no	Out of function for other reasons, no
1964	3	0	2	1	0
1 65	21	5	12	2	2
96(	30	7	17	2	4
1 ?,	3	11	14	6	1
1) 8	30	8	19	3	0
1 69	8	14	12	1	1
1970	30	11	14	3	2
19 1	6	15	8	2	1
19	5	16	7	0	
1973	7	3	2	1	1
Sum	3	90	107	21	14

6 replaced. The two perforations with Cordis electrodes occurred during placement of the elec trode and was immediately corected, without any untoward effect to the pat ent. The perforation w th a Stanium electrode which led to loss of capture after a few days, was verif ed on heart X ray The electrode was left in situ and a new electrode inserted.

Late complications, i.e after 3 months function time are shown in Table III The five fractures of Cordis electrodes are specified in Table IV Four of these occurred among the first electrodes of this type implanted in this hospital (i e electrode number 1 3 10 and 2) The fifth in a patient who also had a thrombus of the right subcla ian vein provoked by heavy exercise and in whom those two incidences probably were related Since January 1974 the electrodes have been anchored with a butterfly clamp just outside the ein. In 2 of the 4 early electrode d slocations after this time it appeared on re-operation that the anchoring had failed and the lead was wound up around the pulse generator in the pacemaker pocket Twidd lers syndrome) Two Metronic electrodes of the flange-less option Model 6909 was used one of them introduced via a Hoffman Des let introducer nto the subclavian vein. One of these patients d ed suddenly after 16 days, the other after 2 months Another electrode of this type introduced in January 1975 dislocated twice during the first 24 hours, to the pulmonary artery and right atrium respecti ely

Failu e f connectı ns bet een pulse generator and lead

The incidence of failure of connections is related to the number of operations on pulse generators

T b II 3 II Failur Elem EMT 588 electrod s Lead b er ation tim

Observation time (years)	Cumulative no of electrodes	Number of failures	Miscellaneous	Deaths no
			Causes for electrodes terminated	
0	232	4	2	11
	13	4	4	15
1	192	3	2	23
2	161	2	3	23
3	118	0	2	11
4	86	3	0	7
5	68	3	0	6
	47	1	1	6
	22	1	0	3
8	13	0	0	2
9	5	0	0	0
SUM		1	14	107

for different pacer-electrode systems in Table VIII Failures in the connecting system occurred in 2½ per cent of all pulse generator implants. More detailed information is listed in Table IX. The system with Cordis pacer and Elema lead had a high incidence of increased resistance in the connection. Four of these cases, however were discovered on impulse analysis before pacing failure occurred. Cordis has now introduced a new adapter for Elema leads. The failing Elema systems were all from an early period with an old connection system, and before the method with photoanalysis of the pacemaker impulse had been brought into use

Total number of re-operations due to problems with electrodes, leads or connections

In this retrospective analysis it has been evident that problems with electrodes, leads and connections are not uncommon Of a total of 362 patients, 77 (21 per cent) had had one or more extra operations after implantation of the pulse generator due to problems with electrodes, leads or connectors Fortyfour of these operations, in 36 patients were due to early electrode complications during the first 3 months. Late electrode complications were the reason for 29 operations. Nine of these were, however probably related to previous replacement operations for pulse-generator Five were fractured Cordis lead and 15 various operations on the Elema EMT 588 leads. Twenty-two operations in 21 patients were due to failing connections between lead and pulse generator. Thus, in only 20 of these 77 patients were re-operations strictly related to late electrode complications per se and twelve of these operations occurred during the first year

Table VIII Incidence of failure in the connection between pulse generator and electrode related to number of operations for implantation of pulse-generator

Pulse generator and electrode, type	No of failures	Total no of operations	Incidence of failures per operation, per cent
Cordis/Elema	11	239	5
Medtronic/Elema	3	187	2
Elema/Elema (Old system)	4	133	3
Cordis/Cordis	3	131	2
Medtronic/Medtronic	0	69	0
Stanicum/Stanicum	1	14	7
Stanicum/Elema	0	2	0
Sum	22	797	2.5

DISCUSSION

In this retrospective study 232 Elema EMT 588 soft endocardial electrodes and 135 unipolar stylet endocardial electrodes (Cordis, Medtronic, Elema EMT 28-, Stanicum) have been followed. Sixty eight of the Elema EMT 588 electrodes have been followed for 5 years or more. Special emphasis has been laid on the durability of this electrode. The occurrence of electrode complications has been related to replacement operations for pulse generators.

In the EMT 588 electrode wirebreaks were all probably related to replacement operations for pulse-generators. They were located either in acute bends of lead in the fibrous tissue near the pacemaker pocket or near a wire splice. An improved operating technique avoiding loops of excessive pacer wire near the pulse generator may reduce the incidence of this complication One of the defects in insulation was also clearly related to operation for replacement of pulse-generator while the other three insulation defects probably were caused by too tight holding sutures Defects in insulation of

Table IX Failure in connection between pulse-generator and electrode specified

System	Type of failure	No cases
Cordis/Elema	Inadequately insulated set screw	2
	Lead loosened	1
	Broken splint (in old type plug)	2
	Not specified	6
Medtronic/Elema	Lead loosened	1
	Insulation of set-screw forgotten	1
	Not specified	1
Elema/Elema	Lead loosened	4
Cordis/Cordis	Broken splint (in old type plug)	1
	Lead loosened	1
	Inadequate splice of new terminal	1
Stanicum/Stanicum	Fracture between lead and connector	1

il s type may be avoided if holding sutures are t ghtened too hard or if an extra silicon sh ld is placed under the anchoring sutures Of l la electrode dislocations and exit blocks 8 e probably provoked by operations for replace m ot pulse genera ors. The incidence of such aplica ions will in the future probably be reduc he ntroduction of long life pacers

MT 58 w re is made of 4 steel filaments l around a terylene core During replacement ations for pulse genera ors we have observed hi terylene ore often has developed a brown ouration at the open end which has been i nted to the pacer probably due to introduc n f moisture Two electrodes were replaced s ely for th s reason We feel that the possibility an not be excluded that the terylene f ber acts as a w ck, which by apillary attraction will lead moisture through the whole wire if a small leak exists in the onnect on between pacer and lead. We fear that th effect probably may be the reason fo some f the late exit blocks which app ar d some months after pacer replacement operations in previously stable electrodes

Our over all incidence of late complications with the EMT 589 electrodes is about the same as those reported in the l terature by others (6 13) We conclude that many of late electrode complicat ons are related to pulse generator re placement operat ons An Elema EMT 589 elec trode which has been positioned without complica tions and which is not disturbed by re-operations for f stulae o pacemaker replacements seems to have h gh degree of reliability in long term permanent pacing

Th two-step procedur w th Elema EMT 588 electrodes was abandoned in th s hosp tal because the patients had to be hospitalized 1— week longer when th s method wa used The ncidence of electrode correction with this method prior to implantation of pulse generators was h gh, partly because many of the electrodes were corrected when the threshold value exceeded 4 or 5 Volts, partly due to electrode dislocations. Some of the latter w feel occurred because the electrodes were pulled out

The electrode w h helical spring coil wire of the type Cordis, Medtronic Elema EMT 282, and Stanium has only been observed for a few years in this hospital and their long time durabil ty can therefore not be evaluated in this series. The incid ence of wirebreaks seems however to be consider ably higher than for the EMT 588 electrode. In the latter 3 breaks occurred, i e one per 217 pacing years, wh le in the former 5 breaks occurred, one per 37 pacing years In reports from the *literature the incidence of wirebreaks in con* ent onal electrode systems has been from 0 to 4 per cent (4 9 11 15) Lead breaks in the EMT 589 electrode seems to be infrequent ((13) From the l terature i is postulated that wirebreaks always occur between the entrance of vein and the pacer (9) and usually either in acute bends or near a fixation point as for instance the vein, the connection to pulse generator or a splice (11) Defects in insulation or wirebreaks may be provok ed by abrupt movements (10) The inc dence of lead breaks may be reduced by improved technique (11)

Fixation of the wire outside the vein with a butterfly clamp may prevent the electrodes being pulled out and coiled up around the impulse generator During the last year when we have used this fixation systematically of the 4 early electrode d slocations were related to fa lures in th e fixation method A flange near the electrode t p will probably anchor the electrode in the right entricle At l ast our experience with a flange-less opeton, one ex t block, one d slocation, and one sudden death in 3 cases indicate that this is so.

It is not possible from this material to decide wh ch is the better of the EMT 588 electrode and the con ent onal because the observation time of the latter is too short. The pos tioning of the EMT 588 electrode in the conventional way with the patient n the left lateral position is in our experi ence not always easy but by means of a guiding theter the electrode can be placed with the patient i he supine position (14) We ha e no experi ence w th this latter method. Con entional elec tr des are asier to introduce into the right ent l but the r sk for perforation of the heart greater although serious untoward effects from

this complication seem to be infrequent (1 2, 12) Conventional electrodes can easily be manufactured with small tips which require less current for stimulation and are therefore suitable for use with low current pulse generators. An example is the Cordes ball tip electrode Light tip electrodes of the EMT 588 type have been reported not to be very successful (16) In our experience the EMT 588 electrode has demonstrated its durability Many of the late complications are probably secondary to operations for pulse generator replacement, and will therefore be avoided when long lasting pulse-generators in the future will hopefully be in common use.

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Complications with Permanent Endocardial Electrode Systems

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ABSTRACT

The different types of endocardial electrode systems in 185 patients during the last twelve years are discussed. The surgical technique for the new method used cephalic vein is described. The electrode systems used in the last 2 implantations there has not been any displacements or retractions. Of the total number of patients only 4 required replacement of endocardial by myocardial electrodes. This was caused by unstable position and high stimulation threshold. Fracture of the electrode occurred in 4 cases. Stimulation of the diaphragm occurred in 10%, displacement and retraction of the electrodes in 6.5% and heart penetration or perforation in 3.8% of the patients. There was one death from cardiac tamponade due to electrode perforation of the right ventricle. One case had irreversible brain damage due to prolonged asystole during pulse generator replacement. Unimportant wound infections and haematomas occurred in 5 patients and phlebitis in 3 patients. More or less serious electrode complications have been seen in 56 of the 185 patients, 19 patients having more than one complication.

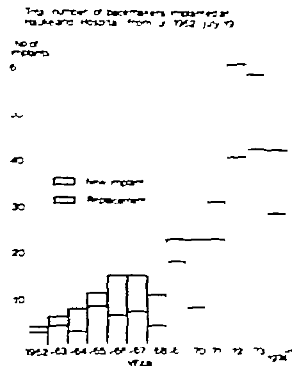


Fig 1

The total number of patients treated with pacemakers at Haukeland Hospital the last 12 years is seen from Fig 1. During the period January 1967 to July 1974 we have only used internal electrodes during pacemaker implantation. 213 electrodes have been inserted in 185 patients.

METHODS:

The surgical technique used in these patients has varied according to the preference of the actual surgeon involved. Earlier the implantations were performed under general anaesthesia but since January 1974 we have almost used local anaesthesia both at the first implantation and frequently during replacement. The external jugular vein was preferred initially. Since January 1974 we have used the cephalic vein as our standard method. In a certain percentage (about 5%) a typical cephalic vein can not be found. In these cases it has always been possible to find another branch of the subclavian vein in the deltopectoral groove. The implantation of the permanent pacemaker is done in one step though several patients have for some time had

temporary transvenous electrode connected to an external pulse generator.

The incision is made at the deltopectoral groove preferably on the non dominant side and is used both for the venotomy and the preparation of the subfascial pocket for the pulse generator. This preparation is performed by sharp dissection and the pulse generator is placed medial and cranial to the central part of the breast. The electrode is introduced by the help of the guidewire which is withdrawn about 2 or 3 cm. Immediately after the ein has been entered, and is angled about 30 degrees 3 cm from the tip. Introduction to the right ventricle is controlled by fluoroscopy in one plane.

A correct position is determined from ECG recordings from the tip of the electrode after withdrawal of the guidewire and through sensing and stimulation threshold measurements. The length of the intravenous electrode is varied in such way that there is smooth curve intracardially in diastol and light kinking at the tricuspid valve in systole. The electrode is firmly secured by double ligation to the vein with silk. Antibiotics are not used, but vacuum drainage from the pacemaker pocket has been used routinely.

RESULTS:

The total number of complications can be seen from table I. *Fracture of the electrod* has occurred in 4 patients. In 2 of the patients fracture occurred after 14 and 38 months respectively without any known cause. In the third patient fracture suddenly took place after 17 months when he was carrying a 50 kilogram sack on his shoulder. The fracture must be ascribed to this trauma. Most of the electrode is lying coiled up in the right ventricle and has after 6 years not given any further complications (6). In the 4th patient with an Elema 288/B62 electrode, fracture suddenly occurred after 6 months. Chest X-ray showed that the pulse generator had rotated but a further examination of the electrode pointed to a material defect being the cause f the fracture. In all these patients the external jugular vein had been used (table II).

Displacement and etraction of the electrode has occurred in 10 and 2 patients, respectively. Most f the displacements have been to the right atrium or inferior vena cava shortly after implantation. These complications seem to be more frequent when the cephalic vein has been used as opposed to the jugular veins (table II). *Unstable elect od posi-*



Fig. 2. I tu of the patient the endocardial electrodes are replaced by screw-in electrod (Medtronic 6917). In this cas the perocephoid approach as ed. The tip f he electrod as attached to the anterior all of the right ventricle. Th as done by rotating the electrod approximately three times. The electrode ru ru along retropericardially and subcutaneously down on to the abdominal wall.

tion has given intermittent failure in demand function or pacing in 6 patients. In one of the patients this has been combined with a high stimulation threshold value. The endocardial electrode was replaced with a sutureless screw-in electrode (Medtronic 6917) Fig. 2, and pacing has since been normal. In two of the patients there was too much electrode inserted into the right ventricle during implantation. In one of these patients the electrode position was corrected after 10 months due to failure of demand function. In the other patient the electrode was replaced after 5 years because of failure in stimulating the heart.

In 7 patients the electrogram from he right ventricle had an atypical pattern. This can in 4 of the patients be ascribed to intraventricular conduction defects as the stimulation threshold was low (0.5—1.5 mA). Several positions were tried without any change in QRS-configuration. T

ALL COMPLICATIONS RELATED TO ELECTRODES

IN 185 PATIENTS

ELECTRODES TYPE	NO	FRACTURE	DISPLACEMENT AND RETRACTION	UNSTABLE POSITION OR INCORRECT POSITIONING	TECHNICAL AND SURGICAL FAULTS	CHANGE IN TRESHOLD	STIMULATION OF DIAPHRAGM	PERFORATION OF PENETRATION OF HEART	PERFORATION OF TRICUSPID VALVE	PHLEBITIS	PERFORATION OF SKIN OVER ELECTRODE	WOUND INFECTION ALONG ELECTRODE
MEDTRONIC												
BIPOLAR												
5818	11		1		1	2						
6901	20				2			2		1		
UNKNOWN	7				1				1			
UNIPOLAR												
6905	22		2	1	1	3	3	1		1	2	
6907	44		2	3		1	7	2			2	
6917	2						1					
6913	1											
CORDIS												
322 61	9		2				2	2		1		
322 620	33		2	1		1	2					1
UNKNOWN	40	3	3	2	3	1	1		1		1	1
ELEMA												
265 862	2	1					3	1				1
TOTAL	213	4	2	7	8	8	19	8	2	3	5	3

I H I

patient the electrode was placed n the coronary sinus. Although fluoroscopy n frontal plane seemed to show a orrect positioning, an X ray in lateral position showed that the electrode was placed in the coronary sinus (f g 3a and b)

Different technical nd su gical faults have occurred during implantation or replacement In three cases with Cordis electrodes it has been d fficult to release the elect ode terminal from the pulse generator and it has been necessary to splice the electrode In two other ases with Medtronic 5862-C pacemakers and 6901 electrodes there was inadequate sealing of the connection between pulse generator and the electrode with failure to pace in the course of a couple of days. In one patient with a bipolar Medtronic electrode each of the poles was disconnected from the pulse generator leading to an interruption in the pacing This resulted in asystole lasting several minutes and subsequent irreversible cerebral damage On two occasions it has been difficult to position the electrode in the right ventricle making reoperations necessary

Chang n stimulation threshold and failure of pacing have been documented in 8 patients during a period varying from a few hours to years

COMPLICATIONS WITH POSSIBLE RELATION TO SURGICAL TECHNIQUE IN 200*
PERMANENT PACEMAKER IMPLANTATIONS (185 PATIENTS)

SURGICAL TECHNIQUE	CEPHALIC VEIN	INTERNAL OR EXTERNAL JUGULAR VEIN	OTHER VEINS	STANDARD TECHNIQUE AFTER DECEMBER 1973	TOTAL
NO. OF IMPLANTATIONS	67	62	12	39	200
UNSTABLE POSITION, DISPLACEMENT OR RETRACTION	14 16	2 3%	3%	3%	15
FRACTURE OF ELECTRODE		(3%			3%
WOUND INFECTION		3%)	3%	1%	
HAEMATOMA		6%	3%		
SKIN NECROSIS WITH ELECTRODE FISTULA					3%
SKIN NECROSIS WITH DANGER OF FISTULA	5%)	6%			
THROMBOPHLEBITIS	)	2%			

*TOTAL NE IMPLANTATIONS ARE PERFORMED IN PATIENTS WHOSE OLD ELECTRODES DID NOT FUNCTION SATISFACTORILY OR IN WHICH INFECTION LED TO EXTIRPATION

Table II

after implantation. In two of the patients the high threshold values were possibly caused by extensive myocardial fibrosis. After the implantation of myocardial electrodes no failure in pacemaker function has been discovered. One of the patients died in ventricular fibrillation during an attempt to reposition the electrode. In the other 5 patients pacemaker function has been normal after repositioning or replacing the electrodes.

Stim lation of diaphragm has been a frequent complication, occurring in 19 of 185 patients (10 %). In some the phenomenon has been intermittent and caused little embarrassment due to a demand pacemaker system. In 7 cases repositioning has been tried because of troublesome symptoms. In three out of these seven patients perforation of the heart was strongly suspected because of failure in pacing and a pericardial fric



F g 3a and b The -ray in frontal projection ( ) gives he impr ssion that he electrode lies in the right entricle but the pictur in the lateral projectio (b) indicate that th electrod is placed in the oronary sin ECG ecorded during implantation is ompatibl ith the electrode lying in the coronary sinu



ALL COMPLICATIONS RELATED TO ELECTRODES
IN 185 PATIENTS

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6907	44		2	3		1	7	2			2	
6917	2						1					
6913	1											
CORDIS												
322 261	9		2				2	2		1		
322 620	33		2	1		1	2					1
UNKNOWN	40	3	3	2	3	1	1		1		1	1
ELEMA												
281 862	2	1					3	1				1
TOTAL	213	4	12	7	8	8	19	8	2	3	5	3

TABLE I

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Different technical and surgical faults have occurred during implantation or replacement In three cases with Cordis electrodes it has been difficult to release the electrode terminal from the pulse generator and it has been necessary to splice the electrode. In two other cases with Medtronic 5862-C pacemakers and 6901 electrodes there was inadequate sealing of the connection between pulse generator and the electrode with failure to pace in the course of a couple of days. In one patient with a bipolar Medtronic electrode each of the poles was disconnected from the pulse generator leading to an interruption in the pacing. This resulted in asystole lasting several minutes and subsequent irreversible cerebral damage. On two occasions it has been difficult to position the electrode in the right ventricle making reoperations necessary

Change in stimulation threshold and failure of pacing have been documented in 8 patients during a period varying from a few hours to 2 years

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Displacement of endocardial pacemaker electrodes

A comparison between Elema 588 B and Chardack 5818

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ABSTRACT

The implantation of permanent pacemaker has been carried out on 159 patients suffering from Adams-Stokes seizures. Elema 588 B electrodes were implanted in 119 patients and Chardack 5818 electrodes in 40 patients.

The two types of electrodes differ with regard to both the implantation technique and weight and thickness N difference was found in the incidence of electrode displacement or survival between the two groups similarly the experience of the physician with regard to implantation had no influence on the frequency of displacement

Displacement on the other hand occurred significantly more frequently in those patients suffering from heart disease demonstrable by -ray examination.

Pacemaker treatment of attacks of Adams-Stokes syndrome was first discribed in 1952 when *Zoll* reported his results of external pacemaker treatment of 2 patients treated with one electrode in the oesophagus and one over the precordium. External stimulation was able to carry the patient over the critical phase, but this treatment was unsuitable for long term use owing to the pain it caused

In 1959 *Hunter Roth Bernadez & Noble* treated attacks of Adams-Stokes syndrome with the implantation of electrodes in the myocardium and external stimulation In the same year *Furman & Schwedel* described an electrode that could be introduced into the right ventricle via the external jugular vein. This endocardial electrode could be introduced under local anaesthesia in contrast to the myocardial electrodes.

With the increasing number of elderly patients who are referred for pacemaker treatment the transvenous, endocardial electrode implantation has been seen to be superior to other methods owing to the low primary mortality *(Morris Whalen McIntosh Thompson Brown & Jung 1967 Imparato & Kim 1972)* The endocardial electrode has the one disadvantage that displacement occurs in approximately 20 % of the cases *(Schaudig Thurmayr & Zenker 1971 Imparato & Kim 197)* Several different types of endocardial electrodes have been devised in order to reduce the frequency of electrode displacement. A number of the electrodes manufactured are provided with a collar near the tip of the electrode, others have barbs which can be released and enter the myocardium during implantation

The object of the present work has been to compare the incidence of displacement between two types of electrodes having different thickness and weight.

MATERIAL AND METHODS

The survey includes 159 patients in whom a permanent pacemaker had been implanted during the period 1965—1973, owing to bradycardia presenting symptoms The average age at the time of implantation was 72.4 years.

Two different types of electrodes have been employed for transvenous use, Elema 588 B [1]) and

Criteria for correct electrode positioning.

Anatomical position

) At the bottom of the right ventricle
b) The tip 3—5 cm from the apex of the heart
) A slight curve of the electrode in the right atrium

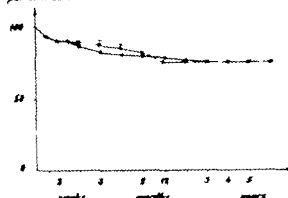
Stable position

) After repeated deep breathing
b) After repeated coughing

Low stimulation threshold

Less than 0.5 mA ~ 1 (measured with an external pacemaker)

Table 1 The table show the criteria sed for ac eptable mplantation of the electrode



F gure 1 *Survival curv for Elema 588 B (○—○) 119 patient and Chardack 5818 (● ●) 40 patient*

Chardack 5818²) The selection of the type of electrode has been secondary in all patients to the selection of the pacemaker One hundred and nineteen patients have had Elema 588 B electrodes implanted and 40 a Chardack 5818 electrode.

The Elema 588 B is a thin, very pliable, unipolar electrode having an external diameter of 1 3 mm. The tip of the electrode weighs 556 mg The electrode is introduced through a guide catheter the later was in our case a shortened Lehman catheter No. 8³)

Chardack 5818 is a bipolar electrod with a diameter of 2 6 mm. The weight of the tip is 725 mg Th Chardack electrode is provided during introduction with two central stilettes, which are removed after insertion of the electrode. Introduction is facilitated by creating various bends in the stilettes and moving them up and down the electrode thus producing bends in the electrode itself

The criteria for ac eptable electrode positioning can be seen from table 1 The patients have been hospitalized for a minimum of 10 days and have been taught daily pulse control After discharge the patients have been controlled in the out-patient department at intervals of 3 months and the pace maker has regularly been replaced every second year providing no complications occurred prior to this date

The term electrode displacement covers cases where the electrode has moved within the right ventricle, displacement of the electrode to the right atrium, pulmonary artery or exit-block without other plausible explanation.

The decrement method *(Bradford Hill 1967)* has been employed in calculating the electrode and patient survival rates. The "Greenwoods estimate *(Cutler & Ederer 1958)* was used when calculating the standard deviation within the various intervals.

The size of the heart has been evaluated from the x-ray pictures of the thorax taken during hospitalization. A cardio-thoracic index of more than 0 5 has been used as the criteria for enlarge ment of the heart.

All the statistical comparisons have been done using 2×n χ^2 test.

RESULTS

No difference was found in the incidence of or the time of the displacement of Elema 588 B and Chardack 5818 (Fig. 1) A total of 38 of the 159 implanted electrodes were displaced (23.8 %) In the first week after introduction 6.8 % of all the implanted electrodes were displaced. Within the first month after implantation 13.0 % of the implanted electrodes were displaced and 21.8 % in the course of the first year Displacement has not been registrered after the electrode had *f*

) Elema-Schonander Ab S-171 95 Solna, Sweden.
) Medtronic, Inc., Minneapolis, 55418 Minn., U.S.A.
) United States catheter and instrument corporation, Glens F lls. 12801 New York, U.S.A

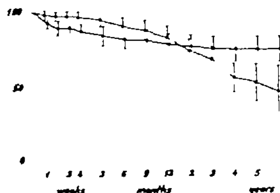


Figure 2. Survival curve for 150 patients with pacemaker (● ●) and survival curve for all the implanted electrodes (O—O) 2p < 0 01

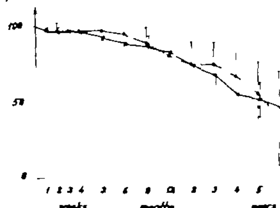


Figure 3. Survival curves for 121 patients without displacement (O—O) and 38 patients with displacement (● ●) of the implanted electrode

tioned for more than 2 years

The survival curve for patients with a permanent pacemaker and the survival curve for all the implanted electrodes are significantly different (p< 0 01) (Fig 2) It can, in addition, be seen that the cumulative survival rate for the patients 5 years after implantation is 52.7 % while the cumulative electrode survival rate 5 years after implantation is 74.2 % Thus 74.2 % of the patients surviving for more than 5 years will only require one electrode implantation.

No difference was found in the survival rates of patients with and without electrode displacement (Fig. 3)

Table 2

experience of the physician	1—10 implantations	11—20 implantations	>20 implantations
early displacement <1 month	20	11	4
late displacement >1 month	13	5	0
total number of implantations	111	63	16

Table 2. The table shows the relationship between the experience of the physician in implantation of pacemaker electrodes and the occurrence of displacement (2p > 0 05)

The experience of the physician with implantation of pacemaker electrodes in relation to the occurrence of displacement is shown in Table 2. This shows a lack of correlation between the experience of the physician and the risk of both early and late displacement. Only the results of the first implantation in a patient are used in the table however experience is based on the total number of implantations performed. The number of implantations per physician varied from 3 to 41 (inclusive re-implantations)

Displacement of the endocardial electrode occurred significantly more frequently in patients with enlargement of the heart 2p<0 05 (Table 3)

DISCUSSION

It is stated that an electrode having a large external diameter and a heavy distal tip is most effected by heart contactions and turbulence in the

Table 3

	normal heart	enlarged heart
+ electrode displacement	9	29
— electrode displacement	55	63

Table 3. The table shows the occurrence of enlargement of the heart and displacement (2p < 0 05)

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Permanent Pacemaker Treatment at Gentofte Hospital

A follow-up Study with Special Reference to Transvenous Electrode Complications, Generator Longevity and Control Procedures.

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ABSTRACT

Results of a follow-up study of 125 patients treated with permanent pacemakers at Gentofte Hospital during the years 1962—1973 are presented. Complications with endocardial electrodes are reported and longevity curves of pacemaker units are given.

The series shows a high frequency of electrode displacement in the first three months and battery exhaustion from the 18th to the 42nd month.

The appearence of complications correlates with the frequences of check up intervals.

In order to predict pacing failure due to battery exhaustion, there would seem to be some merit in carrying out an oscilloscopic display of the pulse artifact in addition to the usual measurement of pulse frequency.

The aim of this retrospective report is, by analyzing a pacemaker series for sudden electrode failures and battery longevity to comment on the value of check-up procedures in an outpatient pacemaker clinic.

MATERIAL AND METHODS

Patients

During the period 1962—1973 permanent pacemaker were implanted in 125 patients. The number of patients paced per year is shown in fig. 1. 74 were males 51 were females, mean age 70.6 and 73.2 years respectively at the time of implantation. Average age 7 years. Age range 35—90 years 42.4 %, 38.4 % and 19.2 % in the age groups <71 years, 71—80 years and >80 years respectively.

Electrodes

Information regarding electrodes implanted before 1967 were inadequate for inclusion in this study. The number of electrodes implanted in the period 1967—1973 is seen in fig. 2. Four different bipolar electrode systems were implanted. 11 epicardial (5814 Medtronic) 130 endocardial (5816 5818 6901 Medtronic). Since January 1972 only the 6901 model has been used for transvenous implantation.

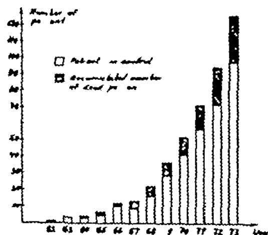


Fig. 1. Number of patients treated with permanent pacing at Gentofte Hospital during the years 1962—1973.

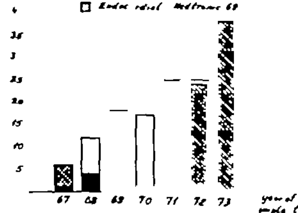


Fig. 2 Number of electrodes implanted from Jan 1967 to Dec 1973 in 120 patients

Epicardial electrodes were implanted through a left sided thoracotomy whereas an infraclavicular approach through the cephalic vein was mostly used for transvenous implantation. Fixation of both electrode and pacemaker unit with nonabsorbable suture was routine procedure during the later part of the period. Units were implanted subcutaneously in the left hypochondrium and the right pectoral region respectively.

Pacemaker units

From 1962 to 1968 a total of 20 fixed rate pacemaker units were implanted. From 1968 when the QRS-inhibited pacemaker was introduced at this hospital, the number of implantations went up by approximately 7 per year and in 1973 a total of 47 pacemaker units were implanted. We have used Medtronic bipolar pacemakers, the QRS-inhibited types 5841, 5842 and 5942, the fixed rate types 5870C, 5910 and 5862. The ratio between the number of QRS-inhibited and fixed rate pacemakers has been about 5:2.

Pacemaker unit longevity

The longevity of Medtronic pacers was analyzed by means of a life-table method (1). Greenwoods estimate was used for the calculation of standard error (2). The material consisted of 115 QRS-inhibited pacemakers (33 5841, 22 5842, 60 5942) and 48 fixed rate pacemakers (28 587C, 6 5910, 14 5862).

Check-up

Patients stayed in hospital for 1 week after transvenous pacemaker implantation. They were seen after 1, 12, 15, 18, 21 and 24 months and then monthly. Before discharge a radiograph in AP and lateral projection was usually taken. At each check-up a brief history was taken by a technician. A 12 lead ECG was recorded for evaluation of pacemaker rate and configuration of paced complexes. Spontaneous activity was noted and the demand function switched off magnetically when necessary. The pulse artifact was not displayed. A clinical examination was done only on request or when special clinical problems existed. Thus, patients were often seen only by the technician. For treatment of non-pacemaker related disease, patients were referred to their GP's.

Pacemaker units were changed when signs of battery exhaustion was demonstrated — generally by a shift in pacing rate. No elective changes were made at a predetermined age limit of batteries.

To illustrate the complexity of the check up of Medtronic pacemakers it can be mentioned that the parameter predicting battery exhaustion of Medtronic pacemakers is different from type to type, and even different within the same type manufactured at different times (12).

Thus, in *Medtronic* pacemakers exhaustion of the battery can generally be detected by measurement of two parameters, i.e. ECG frequency and/or pulse duration. Excepted from this rule is model 5841 where oscilloscopic display of the pulse rise time is the parameter used for check up. Further exceptions are 5862 and 5862C, where no measurement at all allows reliable detection of impending exhaustion.

The models 5842 QRS-inhibited, 5942 QRS-*inhibited (before April 1972) and 5910 fixed rate* (before April 1972) can be checked effectively only by measurement of the pulse duration, which we use as a parameter for these types since January

1974. On the contrary the 5870C fixed rate and the 5910 fixed rate (after April 1972) increases resp. decreases frequency with 5—7 beats/min. as the only reliable sign of impending exhaustion. An increase of pulse duration of more than 10 % and a decrease of frequency of 5—7 beats/min. characterizes the models 5942 QRS-inhibited (after April 1972) and 5944 QRS-inhibited.

Follow-up period

The observation period of pacemakers and patients ranged from March 1962 to January 1974. For electrodes the observation period was extended to June 1974, which meant that all electrodes were observed for at least six months. Follow-up of patients was 100 %.

COMPLICATIONS

Electrode failure

Only electrode complications which caused failure of pacing were analysed, i.e. electrode displacement (verified radiographically or during fluoroscopy), exit block (an unexplained elevation of threshold above pacemaker output) and myocardial perforation (verified at autopsy or at operation). A single case of electrode induced ventricular fibrillation was included, whereas no example of cable breakage was noted in 130 endocardial electrodes. The epicardial electrode complications are not reported here as our series is very small. However it can be stated that a significant number (mostly cable breakage and exit block) followed epicardial implantations.

Electrode displacement

Endocardial electrode complications leading to failure of pacing appear in table I. Displacement was *frequent in the three months following implantation*. Two late displacements occurred during change of pacemaker unit due to battery exhaustion. The changes were covered by transvenous temporary pacing as there was no spontaneous ventricular activity. The manipulations with the temporary electrodes caused the displacements according to records. Two other late failures were caused by

Table I. Time distribution pattern of endocardial electrode complications leading to failure of pacing

Time in months	Displacement	Exit block	Perforation	Arrhythmia	Total
0—¼	6	5	2	1	14
¼—1	7	—	—	—	7
1—3	7	—	—	—	7
3—6	1	—	—	—	1
6—12	1	1	—	—	2
12—18	1	2	—	—	3
18—24	2	2	—	—	4
24—30	—	—	1	—	1
30—36	1	—	—	—	1
36—42	1	—	—	—	1
43—48	—	1	—	—	1
Total	27	11	3	1	42

"twiddlers syndrome". This complication has been totally eliminated in the later part of our series, (61 Medtronic model 6901 implanted since January 1972) in which we have seen one late displacement only. The frequency of electrode displacement in our early series (to January 1972) is 27 % in our late series 13 % (to June 1974). Other centers have reported on electrode complications (3, 5, 6, 7).

Exit block

Exit block (unexplained elevation of stimulation threshold) counted for 11 (25 %) of electrode complications leading to failure of pacing (table I). Also late exit blocks were seen.

Perforation of myocardium

In three patients penetration of the right ventricular wall was diagnosed. One died from haemopericardium, one had a new electrode and one had the electrode retracted to a stable position.

Arrhytmia

A single case of electrode induced ventricular fibrillation — preceded by premonitory ventricular ectopic beats — was seen on the second post implantation day. The arrhythmia was immediately

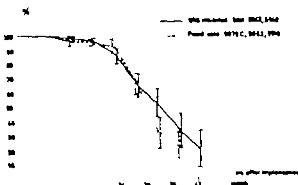


Fig. 3 Function time for 115 Medtronic QRS-inhibited pacemaker-units (33 5841 22 5842 60 5942) and 48 fixed rate units (28 5870C 6 5910 14 5862) Calculated by means of life table method using Greenwood estimate (1,2) Vertical bars indicate ± SE.

converted by DC shock. After removal to a less irritable position, satisfactory pacing was re-established. Serum potassium was normal.

Table II The distribution pattern of deaths caused by electrode or pacemaker unit as well as deaths from unknown reasons

Time in months.	Number of deaths caused by electrode failure	Number of deaths caused by pacemaker unit	Number of deaths from unknown reasons.	Total
0—¼	1	—	—	1
¼— 1	—	—	1	1
1— 3	2	—	—	2
3— 6	—	—	—	—
6—12	—	1	—	1
12—18	1 (separ)	—	—	1
18—24	2	—	—	2
24—30	—	1	—	1
30—36	—	—	—	—
36—42	—	—	—	—
42—48	—	—	—	—
Total	6	2	1	9

Infection

Reports on pocket and electrode infections are not included in this study

Pacemaker unit longevity

The battery lifetime of Medtronic pacemakers in our series is shown in fig. 3 Of 115 Medtronic QRS-inhibited pacemaker units (33 5841 22 5842 60 5942 90 % were in function after 18 months, while 40 % were pacing after 3 years. Of 48 fixed rate units (28 5870 C, 6 5910 14 5862) 95 % were functioning after 18 months and 25 % after 3 years (4, 8)

Mortality

The postoperative mortality (within one week of surgery from all causes) following transvenous implantation was 2 4 % Only a single death (0.8 %) could be attributed to pacing per se A total of 28 patients died in the observation period. 19 of these from known causes unrelated to failure of pacing. 5 patients died from electrode complications (1 hemopericardium, 4 electrode displacement) (Table II) The first one died on the day of operation as a result of cardiac tamponade Another one had an early electrode displacement but refused reoperation. He died two months later A third patient was brought to hospital with Adams-Stokes seizures. Before correction of electrode position he suffered a fatal cardiac syncope. The fourth and fifth patients had the electrode tip inserted near the tricuspid valve. They had both been observed in hospital on acount of intermittent failure of pacing. As pacemaker function stabilized during hospitalization, the decision to correct the electrode position was postponed. The patients were seen seven and one day before death respectively both with normal pacemaker function. Displacement was verified at autopsy in one case.

Two deaths were possibly caused by the pulse generator One by fixed rate pacing in the T wave, which was observed repeatedly before discharge. Another one probably from battery exhaustion (insufficient control of the first patient in our series in expectance of a 4—5 year battery life time)

One patient died suddenly and unexpectedly one day after discharge from hospital following an uncomplicated pacemaker implantation procedure. The possibility of an electrode failure cannot be

dismissed even if there was no positive evidence for this.

Finally one patient died from sepsis caused by pacemaker pocket infection.

DISCUSSION

It is significant that literally all patients with electrode complications were brought to hospital either by symptoms or by routine check-up in due time to prevent serious consequences of failure. In three cases, however, the significance of a known electrode malposition/malfunction was not recognized at the time of check-up or hospitaliza tion, and turned out to be fatal. Thus our time pattern of checking-up seems reasonable with regard to evaluating pacemaker function

On the other hand it is possible that a high rate of early electrode complications should be correlat ed with frequent early check-up (10) in combina tion with implantation of pacemaker units, which allow non-invasive threshold testing. Measurement of stimulation threshold as practiced with these units, gives hope of diagnosing impending elec trode failure (9) From the information in table I it is seen that during the first three postimplanta tion months there are many electrode complica tions. In the second period (3—18 months) the endocardial system is fairly stable and battery depletion has not begun as yet (fig. 3) giving a low complication frequency From the 18th month the batteries start to deplete until 60—75 % of pacers are depleted by the third year Thus time pattern of electrode complications and battery life time justifies in our view a similar time pattern of check-up in our pacemaker clinic, i.e

1 2—3 check-ups in the first three postimplanta tion months until electrodes and stimulation thresholds are stable (11) The benefit of these early controls probably depends on the use of pacemaker systems, which allows non-invasive testing (9 10)

2 few check-ups in the second period where elec trodes are stable and the performance of bat teries is steady

3 increasing frequency of check-up in the third period on account of battery failure. To con- firm whether a given change of pacemaker rate is due to exhaustion of batteries, oscilloscopic display of pulse duration should be arranged. For certain types of pacemakers, the pulse duration (or pulse rise time) is the primary parameter to control, as a decrease of pulse width (or an increase of pulse rise time) is the first sign of exhaustion (12)

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Complications of transvenous and transthoracic electrodes

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ABSTRACT

Electrode complications in a series of 220 patients are presented. At the primary pacemaker implantation, 114 patients received transvenous and 106 transthoracic electrodes For the transvenous technique the Elema unipolar electrode (EMT 588 and 588 B) was used exclusively and for the transthoracic technique an epicardial disc electrode (EMT 567) was used in 64 per cent and myocardial electrodes (Vitatron MIP 125 Medtronic 5814 and 6913) in 36 per cent. The material was followed up for an average of three years (from 2 to 10 years)

The dislocation frequency of transvenous electrodes was 10 4 per cent/patient year as 21 per cent of the electrodes became dislodged. Of the electrode dislocations, forty per cent occurred within the first post implantation month. Exit block at stimulation with transthoracic electrodes was seen in 8 1 per cent/patient year Infections were more common with the transvenous than with the other types of electrodes.

The myocardial electrode was significantly ($p < 0.05$) more reliable than the transvenous electrode during the follow up evaluated in terms of uncomplicated function time of the primary electrode.

As in Helsinki both endocardial and myocardial epicardial pacemaker electrodes have been used it seems to be of interest to report the results from our pacemaker material.

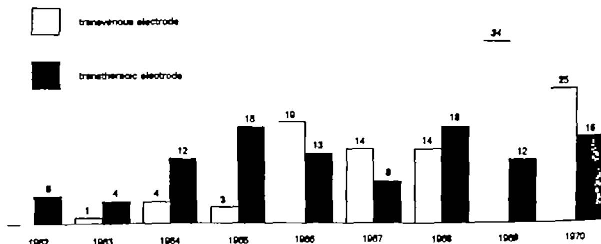


Fig 1 Annual numbers of pacemaker implantation

MATERIAL AND METHOD

Cardiac pacemakers were implanted into 470 patients at the Department of Thoracic Surgery, Helsinki University Central Hospital, in 1962—73. In this report, pacemaker systems implanted 1962—70 and followed up to the end of 1972 are presented. This series consisted of 220 patients: 114 received a transvenous and 106 a transthoracic electrode at the primary pacemaker implantation. Fig 1 shows the annual number of patients with a transvenous or transthoracic electrode at the first pacemaker implantation.

The Elema unipolar endocardial electrode was employed exclusively for the permanent transvenous pacing. The implantation was carried out in two phases: firstly, the permanent transvenous electrode was introduced into the apex of the right ventricle through the basilic and axillary vein in 57 per cent, jugular vein in 32 per cent and cephalic vein in 11 per cent of the patients; secondly, one week later, the pulse generator was implanted.

An Elema epicardial disc electrode (EMT 567) was used in 64 per cent, Vitatron myocardial loop electrode (MP 125) in 21 per cent and Medtronic myocardial coil electrode (5814 and 6913) in 15 per cent of the patients for the transthoracic pacing. Electrodes were implanted through a left anterior thoracotomy in 58 per cent, epigastric mediastinotomy in 34 per cent and parasternal mediastinotomy in 8 percent of the patients.

Table 1 Ordinal number of the electrode at the end of the follow-up grouped according to the first pacemaker implantation

	First implantation			
	Transvenous		Transthoracic	
	No of cases	%	No of cases	%
1st electrode	78	68	79	75
2nd electrode	25	22	1	16
3rd electrode	8	7	7	7
4th electrode	3	3	3	3

The follow-up of the cases began at the implantation of the pacemaker and continued as long as the patient was under the control of this hospital or to the end of the year 1972. The analysis of electrode complications was made retrospectively.

RESULTS

The material was followed up for between two and 10 years, average three years. Table 1 shows the ordinals of electrodes at the end of the follow-up in the primary transvenous (TV) and transthoracic (TT) groups. Electrode re-implantations during the follow-up are collected in Fig 2. Electrode re-implantations were performed in 90 occasions, in 37 with a transvenous and 53 with a transthoracic electrode. Thus at the end of the follow-up 100 patients were equipped with transvenous and 120 with transthoracic electrodes. Taking into account electrode re-implantations and

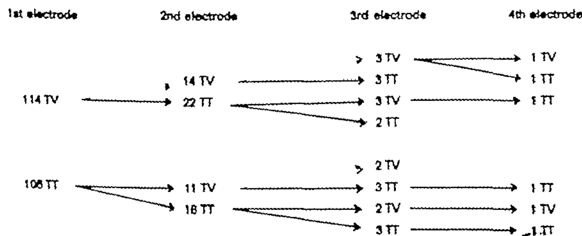


Fig 2 Technique of electrode re-implantation

Table 2 Electrode complications during the follow-up

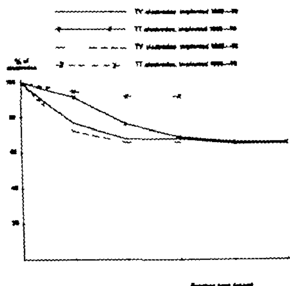
Complication	Electrode: Transvenous No of cases	Transvenous Frequency %/patient-year	Transthoracic No of cases	Transthoracic Frequency %/patient year
Pacing failure	35	11.8	32	8.1
Dislocation	31	10.4	—	
Exit block	4		32	8.1
Technical failure	9	3.1	15	5.8
Wire break	2		6	
Insulation break	5		6	
Electrode loosened from heart	—		3	
Electrode loosened from pacemaker	2		—	
Infection/Fistula	36	12.2	24	6.1
Electrode	9		4	
Pacemaker pocket	26		20	
Sepsis	1		—	
Total	80	27.1	71	18.0

the folow-up periods, the size of the transvenous paced material was 297 patient years and the transthoracic paced material 395 patient years.

Table 2 presents the electrode complications during the follow-up Dislocations of the transvenous electrodes occurred from nine to 480 days (mean 122 days) after the implantation. Forty per cent of the electrode dislocations occurred within the first month and 84 perc ent within six months Dislocation refers here to loosening of the tip of transvenous electrode from the endocardium of the right ventricle Exit block of transvenous electrodes may include undiagnosed electrode perforations. Subsequently we have seen perforation of the Elema unipolar transvenous electrode through the wall of the right ventricle in 3 similar cases at implantation of a myocardial electrode. Exit block of transthoracic electrodes, undiagnosed dislocation, fibrosis and so forth, developed from one week to 4 years and 7 months (mean 581 days) after the implantation. Exit block developed in one patient within one month of the implantation Thirty four per cent of the exit block cases were discovered within the first year In 84 per cent of the cases with exit block developed with Elema epicardial disc electrodes. In this material, exit block developed in 30 per cent of the Elema disc electrodes and in 8 perc ent of the myocardial electrodes.

There was no difference as regards technical failures 3.1 per cent/patient year in the TV and 5.8 per cent/patient year in the TT material. Primary wound infections and infections in connection with the pacemaker or electrode fistula occurred during the follow up in 12.2 per cent/patient-year of the transvenous and 6.1 per cent/patient-year of transthoracic paced patients.

The reliability of the electrodes was evaluated in terms of the uncomplicated function time. Cumulative function time curves (Fig 3) were plotted for the cumulative proportion of primary electrodes still functioning after a certain period of follow-up The proportions were calculated by the life table method (Cutler and Ederer 1958) By this criterion, transthoracic electrodes were significantly ($p < 0.05$) more reliable than transvenous in both the total material and the material for 1968—70 when a year had



F g 3 Cumulativ [illegible] f nction time f electrode

elapsed from its implantation (figure 3) In the material for 1968—70 the transthoracic electrodes, exclusively myocardial, were significantly ($p < 0.05$) more reliable than the transvenous also after the second and third post-implantation year

DISCUSSION

The weak point of transvenous electrode is the tendency to dislocate from the apex of the right ventricle. In the present series the dislocation f equency 10 4 per cent/patient year was in per cent terms 21 perc ent (31/151) which is a little h gher than on an average in the literature. The dislocation frequency in the materials of authors with broad experience such as Edhag (1969) was 17 per ent (45/260) Slaberli et al. (1972) 17 per cent (34/199) and Schaudig et al. (1971) 19 per cent (75/396) The higher infection fre quency of transvenous electrodes here may be elated to the two stage implantation technique.

The high f equency of exit block in this material f transthoracic electrodes arises from the Elema epicardial disc electrodes used in 64 perc ent of the transthoracic implantations. This type of elec trode has a relatively high pacing threshold because of the broad contact area giving a low current density Beside this fixation is unstable on the epicardium (Thalen et al. 1971) Exit block because of high pacing threshold is no problem when myocardial coil or loop electrodes are used. Today the operative risk for transthoracic electrode implantations is not high. The operative mortality rate for the implantation of a myocardial electrode through a parasternal mediastinotomy incision has fallen to the level of 0—3 per cent (Dixon et al. 1972 Garcia and Bengochea 1972 Jude et al. 1969 Morris and Judge 1969) The mortality rate in all 340 surgical procedures of those series was 1 2 per cent (four patients)

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Experiences with a new myocardial electrode for permanent cardiac pacing

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ABSTRACT

The first experiences with a new myocardial sutureless screw in electrode for cardiac pacing are reported. A brief description of the technique is given. The electrode can be inserted quickly and safely under direct vision through a small anterior thoracotomy using a special inserter tool The heart can be brought under pacemaker control in less than 5 minutes The technique was employed in 15 patients. Results to date are promising and it is suggested that this method should be resorted to in cases of unstable pacing or recurrent dislocation of an endocardial lead, or when there are difficulties in the proper positioning of an electrode transvenously

In Sweden endocardial electrodes for transvenous insertion predominate. In many countries, especially the U.S.A there is extensive experience of epi or myocardial pacing leads (2, 4, 5) Some authors consider epicardial pacemakers safer than endocardial pacemakers for permanent cardiac pacing (8)

We have observed defective or unstable pacing with an endocardial electrode in a high proportion of patients in our series early after the implantation and even after many years of perfect pacing When there are problems with an endocardial lead an epi or myocardial electrode can be used This paper reports experiences with a new sutureless myocardial electrode (Medtronic model 6917)

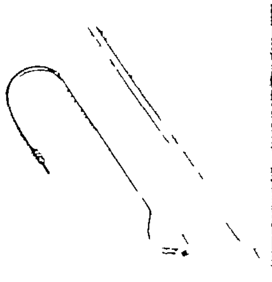
MATERIAL

The transvenous technique has been used as the first method for implantation of a stimulating electrode in patients with non-surgical heart block. Endocardial electrodes were implanted in 1973 and 1974 in 320 new pacemaker patients Re-operation was done in 81 patients (25 per cent) due to poor position of the electrode, recurrent dislocation, pacing or sensitivity problems, infection etc. More than two adjustments were performed in 20 cases. In 15 patients where endocardial pacemaker systems did not work satisfactorily a new myocardial sutureless electrode was implanted through a small thoracotomy There were 10 men and 5 women. The average age was 65 5 years. Three patients were above 80 years.

TECHNIQUE

The electrode and the special accessories are shown in fig 1 and fig 2. The tip of the electrode is coated with silicone rubber except for the last 3/4 turn, which is the stimulating portion of the electrode The electrode is screwed into the myocardium

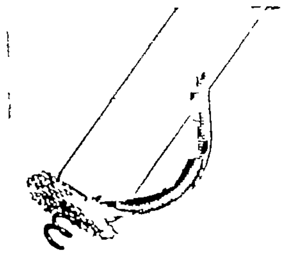
Additional anchoring is provided by a Dacron mesh netting at the base of the electrode bead. The mesh attaches to the ventricular surface by inducing connective tissue formation. The implantation technique is shown in figures 3 4 and 5 The electrode should be screwed into the myo-



F g 1 The electrod model 6917 ith pecial handle which is sed to screw in the electrod into the myo- ard um and tun eler



Fig 3 The lead i affixed to the myocardium ith three clockw turns.



F g 2 The electrode head mounted on the handle



Fig 4 The electrode head ith the Dacron mesh at the base ha been affixed to the myocardium The lead i peeled from the handle and passed using the tunneler to the pacemaker pocket.

cardium during systole to avoid the risk of forcing the electrode through the myocardial wall The selected ventricular attachment site should be an avascular area free of infarcts and fibrous. The lead is passed subcutaneously to the pacemaker pocket with a special tunneler A very small inci sion in the thoracic wall is required. The peri-cardium is adapted with a few sutures and the pleural cavity drained with a tube. No myocardial incision or sutures are required.



Fig 5 A ery limited anterior left-sided thoracotomy required The pleural avity i d ained with ubber t be



Fig 6 Ch st radiogram (side ew) from patient ith an atrialtriggered pac maker T myocardial electrod

RESULTS

An x ray film from a patient with an atrial triggered pacemaker is shown in fig. 6. The patient has two myocardial electrodes one of which is a reserve electrode. The detector electrode was placed in the mediastinum by mediastinoscopy The indication for implantation of a myocardial electrode was defective pacing with an endocardial pacemaker system despite adjustment of the electrode position in 13 cases, and difficulties in proper positioning of an endocardial electrode in two cases. At the time of operation the threshold was 1 volt or less in 11 cases, 1—2 volts in 3 cases, and 4 volts in one case Unipolar threshold should not exceed 2 volts. High threshold primarily may be due to the electrode having been placed in a fibrotic area of the myocardium or the electrode having been screwed in too deeply so the stimulating tip of the electrode enters the cavity of the ventricle One patient was given an atrial-triggered pacemaker the others QRS-triggered or QRS-inhibited pacemakers The patients have been follow up for from a few days to one year Sensitivity problems were observed in one case. The pacemaker was changed to a QRS-triggered type, which has functioned well. Defective pacing has not been observed

One patient was re-operated becauses of bleeding from at small pericardial artery In one patient with a myocardial infarction proper placement of an endocardial electrode could not be achieved. There was a fall in blood pressure and the operation was discontinued. Despite intensive care she did not improve and because of very slow heart rate it was decided to implant a myocardial electrode in this poor-risk patient. There was blood in the pericardium and a perforation of the heart was found at operation, but without current bleeding. She has been observed for a few days only after the operation One patient became severely decompensated postoperatively He had symtoms of a myocardial infarction and during the attempt to insert an endocardial electrode recurrent asystole occurred. The decompensation was treated successfully The patient left hospital two months after the operation in good condition but he died suddenly one week later Postmortem examination showed severe arteriosclerosis of the coronaries but no other finding which could explain sudden death. The other patients are alive with wellfunctioning pacemakers.

DISCUSSION

Implantation of Medtronic's new myocardial screw-in electrode is a very simple and rapid method of achieving stable pacing. Less than 5 minutes is required to open the chest and implant the electrode. The whole procedure takes no more than 30—40 minutes for an experienced surgeon. There is no difficulty in positioning the electrode properly. In the beginning we implanted two myocardial electrodes despite using a unipolar pacemaker system. Nowadays we do not implant a reserve electrode. We prefer a small thoracotomy but other approaches have been described, by which the implantation can be performed under local anaesthesia (1, 3, 7, 9). Good experience with this type of electrode has been reported by other authors (2, 6, 7, 9). However the hazards of thoracotomy for the insertion of permanent epicardial leads have been well documented in the litterature (2, 4, 5, 9). Based on reports in the literature and on our own experience we use the new myocardial sutureless electrode in the following indications:

1. Failure of pacing or defective sensitivity despite two adjustments of an endocardial electrode.
2. In patients who have been referred from another hospital where the position of the endocardial lead has been adjusted twice, we perform one adjustment and if a further adjustment is required a myocardial electrode is implanted.
3. If the patient has two electrodes within the heart and a further electrode is needed a myocardial electrode is used.
4. Unsatisfactory position of the endocardial electrode with the transvenous technique despite one hour's attempt once the tip of the electrode has entered the right atrium if there are no contraindications to thoracotomy.

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nique was performed. The electrode appeared to be *in a perfect position as judged by X-ray*. Tests after operation showed excellent function with a threshold of 0.5 ma. About 3 hours after the operation the pacemaker ceased stimulation. Sensing function was, however, intact and X ray check showed the electrode to be in the same position as at the end of the operation. The following day the patient was reoperated upon for correction of the electrode position. The same threshold was measured. After 3 hours pacing again terminated. Sensing function and the position of the electrode checked by X ray was even this time unchanged. The possibility of exit block was considered and steroids were given without any effect. The operation was repeated for the third time one week later and exactly the same thing happened as at the first 2 operations. After another 9 days thoracotomy and implantation of an epicardial electrode was performed. Bloody fluid in the pericardial sac was discovered and the tip of the electrode was seen to have penetrated the myocardium and pushed out the epicardium for about 3—4 mm.

The later course was uncomplicated and the patient is still enjoying good health and with excellent pacemaker function.

Case no 2 female, aged 77

A pacemaker system was implanted in the patient to correct sinoatrial block with tendency to syncope.

The implantation seemed to be uneventful with *excellent positioning of the electrode and low threshold.*

After 3 days, however following an abrupt movement in the bed the patient experienced stimulation of the diaphragm and loss of pacemaker stimulation of the heart was noted. A repeat operation was performed and also in this patient the position of the electrode seemed to be correct and the threshold was low. Some hours later the same thing happened again and X-ray suggested penetration of the myocardium. Therefore thoracotomy was performed and epicardial electrodes were implanted. Again bloody fluid was found in the pericardial sac and the electrode had bulged out the epicardial layer. The later course was completely uncomplicated and the patient is now in good health with excellent pacemaker function.

Case no 3 female, aged 79

Pacemaker treatment was instituted because of sick sinus syndrome. The first attempt to perform an ordinary pervenous implantation resulted in an excellent electrode position and low threshold as in case no 1 and 2. About 12 hours after the operation the pacemaker stimulation was lost and also the sensing function. X ray showed penetration of the electrode in the lateral part of the apical region. The patient was reoperated upon with primarily excellent result, but some hours later loss of pacemaker function again occurred and X-ray showed a new penetration, this time in the inferior part of the apical region.

Thoracotomy was performed 4 days later without any complications during the operation. Bloody fluid was again detected in the pericardial sac and penetration of the myocardium with bulging of the epicardial layer was found to have occurred. The postoperative course was complicated by pneumonia with respiratory insufficiency. This condition initially responded to treatment, but on the 7th postoperative day the patient suffered an acute extensive anterior wall myocardial infarction and died in cardiogenic shock within a few hours.

DISCUSSION

In series of 63 patients 3 had perforations or *penetrations of the myocardium of the right ventricle. All 3 patients were women, 75 77 and 79* years old and all had primarily excellent pacemaker function. Inadequate pacing as a result of the perforation of the myocardium occurred after a period varying from 3 hours to 3 days after the electrode implantation. All 3 patients survived the perforations, but one patient died one week after the last operation following an acute myocardial infarction. There were no signs of old or recent myocardial infarctions which might have caused the perforations, nor was there any significant enlargement of the heart in these patients. We are well aware that this material is far too small